Physical activity, physical health and clinical phenotype in adults with moderate and severe haemophilia

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Declaration

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Summary

Haemophilia is an inherited bleeding disorder caused by a deficiency in procoagulant Factor VIII (Haemophilia A) or Factor IX (Haemophilia B). Disease severity is stratified according to basal clotting factor levels, as severe (<1%), moderate (1-5%) or mild (>5-<40%) haemophilia. People with haemophilia (PwH), predominantly those with moderate and severe haemophilia (PwMSH), may experience traumatic or spontaneous bleeding into joints and muscles, resulting in significant pain and functional disability. Repetitive joint bleeding in the long-term causes synovitis and osteochondral destruction, resulting in a chronic, degenerative joint disease known as 'haemophilic arthropathy'. PwH who have a severe bleeding tendency are typically treated using regular intravenous administration of replacement clotting factor concentrates in a treatment regimen known as 'prophylaxis'. Prophylactic treatment in PwMSH aims to prevent bleeding and the development or further deterioration of arthropathy. Haemophilic arthropathy causes significant pain and physical disability, which significantly impacts on the quality of life of affected PwH. This particularly affects older adults who had less access to effective treatment as children, in comparison to children and younger adults with haemophilia in the present day who may have better access to improved treatments earlier in life.

PwMSH used to be discouraged from participating in physical activity (PA) due to the increased risk of bleeding and potential joint injury. The improvements in haemophilia treatment over recent decades, however, have enabled PwMSH to become more physically active. PA, with certain considerations for the safety of activity, is now strongly encouraged amongst the haemophilia population due to the numerous health benefits associated with it. PA is beneficial for cardiorespiratory fitness, muscle strength and bone health. It is also associated with a reduced risk of all-cause mortality, obesity and many chronic diseases, such as cardiovascular disease and certain types of cancer. PwMSH may, however, face significant challenges in achieving regular PA due to significant pain and physical disability caused by bleeds and haemophilic arthropathy. They may, therefore, be at an increased risk of various unfavourable health outcomes in the long-term.

The overarching aim of this PhD was to undertake a detailed examination of PA, physical health and clinical phenotype in adult PwMSH in Ireland. To begin, a systematic review is presented in Chapter 1. This review identified variable levels of PA amongst heterogeneous samples of PwH. The majority of studies assessed PA using self-report methods, which are inherently affected by response and recall bias. Furthermore, the relationship between bleeds and PA was difficult to elucidate due to significant heterogeneity amongst study methodologies, as well as incomplete reporting of bleeding phenotype and treatment regimen.

The primary aim of Study I (Chapter 3), was to determine PA in adult PwMSH using combined objective and self-report methods. PA was measured using an accelerometer and a questionnaire. Additional aims were to examine the relationship between PA and age, as well as PA and clinical phenotypic parameters, such as bleeding rate, joint health and treatment regimen. Lower levels of moderate to vigorous PA (MVPA) were demonstrated in PwMSH compared to controls of a similar

age. Participation in various types of PA and sport were reported by both groups. Participation in childhood PA and sport was significantly lower in adult PwMSH compared to controls. No significant relationships were demonstrated between MVPA with bleeding rate, joint health or the age at which prophylactic treatment was commenced.

Considering regular PA is associated with better physical fitness and cardiometabolic health, Study II (Chapter 4) aimed to determine levels of physical fitness and cardiometabolic health risk in PwMSH. Functional aerobic capacity, grip strength and balance were significantly lower in PwMSH compared to controls. Higher rates of abdominal obesity were also identified in PwMSH. There were no significant differences in blood pressure or aortic arterial stiffness between PwMSH and controls, although combined aortic and peripheral arterial stiffness was significantly higher in PwMSH. Lastly, the prevalence of hypertension, insulin resistance and hyperlipidaemia was relatively higher in PwMSH compared to controls.

In light of the findings from Studies I and II regarding lower levels of PA and physical fitness, and increased cardiometabolic risk amongst PwMSH compared to controls, Study III (Chapter 5) was undertaken to explore barriers to PA in PwMSH. Lack of willpower, lack of energy and lack of time were the most common barriers to PA in PwMSH and controls. Lack of resources, fear of injury, lack of skill and social influences were less common barriers to PA in both study groups, although lack of willpower, lack of skill, social influences and fear of injury were more frequently reported by PwMSH. Furthermore, acute pain, chronic pain, frequent analgesia requirements and functional disability were highly prevalent in PwMSH. PA was not significantly associated with pain but age, bleeding rate and the age at which prophylactic treatment was commenced were all significantly increased in PwMSH who reported to have chronic pain. Adults who reported to have functional difficulties were significantly older and less physically active compared to those who denied having functional difficulties.

Lastly, after a period of postponed research activity due to the Covid-19 pandemic, Study IV (Chapter 6) aimed to conduct a follow-up assessment of PA in PwMSH. The impact of the Covid-19 pandemic on PA, function, mobility and pain was also examined. No significant differences in PA measured using accelerometry were found between the original and follow-up time-points. Since the original assessment, the majority of participants reported an increased awareness of PA and a desire to become more physically active. Knowledge of PA guidelines was low, but similar to national average rates. Compared to normal levels of PA engagement, trends in self-reported PA during the consecutive phases of lockdown and eased restrictions throughout the pandemic were variable. PA was reduced compared to normal during the third wave of lockdown, but PA increased in the majority of participants during the third wave of eased restrictions. Pain, access to exercise resources, and maintaining or increasing PA were commonly reported concerns for PA beyond the pandemic.

To conclude, the findings of this thesis highlight that despite a uniform diagnosis, ageing PwMSH present with considerable variation in their physical health profile, potential for multi-morbidity, as well as barriers to PA. In light of this evidence, a ‘one-size-fits-all’ approach to health interventions to address chronic health risk factors may not suffice. Personalised, multi-disciplinary approaches to

health interventions to address lower levels of PA and physical fitness, as well as cardiometabolic risk factors are therefore warranted in future studies in order to optimally improve chronic health risk and quality of life amongst the ageing haemophilia population.

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Publications from this PhD

Peer reviewed publications

- KENNEDY, M., ROCHE S., MCGOWAN M., SINGLETON E., ELSHEIKH E., O'DONOVAN M., RYAN, K., O'CONNELL, N.M., O'MAHONY, B., LAVIN, M., O'DONNELL, J.S., TURECEK, P.L., GORMLEY, J. Physical activity, physical fitness and cardiometabolic risk amongst adults with moderate and severe haemophilia. Haemophilia. 2022; 1- 12 (Original article).
- KENNEDY, M., O'MAHONY, B., ROCHE, S., MCGOWAN, M., SINGLETON, E., RYAN, K., O'CONNELL, N.M., PIPE, S.W., LAVIN, M., O'DONNELL, J.S., TURECEK, P.L., GORMLEY, J., & THE IRISH PERSONALISED APPROACH TO THE TREATMENT OF HAEMOPHILIA STUDY GROUP. Pain and functional disability amongst adults with moderate and severe haemophilia from the Irish personalised approach to the treatment of haemophilia (iPATH) study. Eur J Haematol. 2022; 00: 1– 10 (Original article).
- KENNEDY, M., O'GORMAN, P., MONAGHAN, A., LAVIN, M., O'MAHONY, B., O'CONNELL, N. M., O' DONNELL, J. S., TURECEK, P. L., GORMLEY, J. & THE IRISH PERSONALISED APPROACH TO THE TREATMENT OF HAEMOPHILIA STUDY GROUP. A systematic review of physical activity in people with haemophilia and its relationship with bleeding phenotype and treatment regimen. Haemophilia. 2021; 27: 544-562 (Review article).

Conference presentations/ published abstracts

- KENNEDY, M., O'MAHONY, B., ROCHE, S., MCGOWAN, M., LARKIN, N., O'CONNELL, N.M., LAVIN, M., O'DONNELL, J.S., TURECEK, P.L., GORMLEY, J. No Significant Differences in Physical Activity During the Covid-19 Pandemic in Adults with Moderate and Severe Haemophilia: The Irish Personalised Approach to the Treatment of Haemophilia (iPATH) study (The World Federation of Hemophilia 2022 World Congress, Montreal, 2022- Oral presentation; Poster presentation).
- KENNEDY M., ROCHE S., MCGOWAN M., PATEL A., SINGLETON E., JONES R.C., O'MAHONY B., RYAN K., O'CONNELL N.M., LAVIN M., TURECEK P.L., O'DONNELL J.S., GORMLEY J. Physical activity and cardiometabolic risk profiles amongst Irish adults with severe haemophilia: The Irish Personalised Approach to the Treatment of Haemophilia (iPATH) Study. Haemophilia. 2020;26: 168 (EAHAD Congress, The Hague, 2020- Oral presentation; Poster presentation).
- KENNEDY M., ROCHE S., MCGOWAN M., SINGLETON E., PATEL A., JONES R.C., O'MAHONY B., RYAN K., O'CONNELL N.M., LAVIN M., TURECEK P.L., O'DONNELL J.S., GORMLEY J. Physical activity and haemophilic joint arthropathy amongst adults with severe haemophilia in Ireland: The Irish Personalised Approach to the Treatment of Haemophilia (iPATH) Study. Haemophilia. 2019b; 25: 139 (EAHAD Congress, Prague, 2019- Poster presentation).

- KENNEDY M., MONAGHAN A., ROCHE S., MCGOWAN M., PATEL A., JONES R.C., O'MAHONY B., RYAN K., O'CONNELL N.M., TURECEK P.L., LAVIN M., O'DONNELL J.S., GORMLEY J. 2019a. Barriers to physical activity amongst adults with moderate and severe haemophilia in Ireland: The Irish Personalised Approach to the Treatment of Haemophilia (iPATH) Study. Haemophilia. 2019a;25: 140 (EAHAD Congress, Prague, 2019- Poster presentation).

Other publications

- Megan Kennedy and John Gormley, "Physical Activity during the Covid-19 Pandemic: Insights from the Irish Personalised Approach to the Treatment of Haemophilia (iPATH) Study," Haemophilia.ie: Magazine of the Irish Haemophilia Society (Spring 2022).
- Megan Kennedy and John Gormley, "The importance of physical activity for healthy ageing," Haemophilia.ie: Magazine of the Irish Haemophilia Society (Spring 2020).

List of abbreviations

6MWT Six-Minute Walk Test

α Alpha

ABR Annualised Bleeding Rate

ACSM American College of Sports Medicine

ADLs Activities of daily living

AIx Augmentation index

AJBR Annualised Joint Bleeding Rate

AP Anterior-posterior

AS Arterial stiffness

BBAQ Barriers to Being Active Quiz

BC Body composition

BIA Bioimpedance analysis

BMI Body Mass Index

BP Blood pressure

bpm Beats per minute

CFCs Clotting factor concentrates

CG Control group

cm Centimetres

COR Completeness of reporting

CPAQ Children's Physical Activity Questionnaire

cpm Counts per minute

CRF Cardiorespiratory fitness

CT Computed X-ray Tomography

DBP Diastolic blood pressure

DLW Doubly Labelled Water

DXA Dual-Energy X-Ray Absorptiometry

EHL Extended half-life factor

FVIII Factor VIII

FIX Factor IX

FM Fat mass

h Hours

HA Haemophilia A

HB Haemophilia B

HC Hip circumference

HCV Hepatitis C Virus

HG Haemophilia group

HIV Human Immunodeficiency Virus

HJHS Haemophilia Joint Health Score

HLD Hyperlipidaemia

HR Heart rate

HR_{max} Maximal heart rate

HRR Heart rate reserve

HTN Hypertension

Hz Hertz

IC Indirect calorimetry

ICC Intraclass correlation coefficient

ICF International Classification of Functioning, Disability and Health

iPATH Irish Personalised Approach to the Treatment of Haemophilia

IPAQ International Physical Activity Questionnaire

IQR Interquartile range

IR Insulin resistance

kg Kilograms

kg/m^2 Kilograms per metre squared

LTM Lean tissue mass

LPA Light physical activity

m Metres

MAQ Modifiable Activity Questionnaire

MET Metabolic equivalent of task

mins/wk Minutes per week

ML Medio-lateral

mm Millimetres

mmHg Millimetres of mercury

MPA Moderate physical activity

MRI Magnetic Resonance Imaging

MVPA Moderate-vigorous physical activity

NHF National Hemophilia Foundation

OLST One Leg Stand Test

PA Physical activity

PAGAC Physical Activity Guidelines Advisory Committee

$_{pred}VO_{2max}$ Predicted maximal volume of oxygen consumption

PRIMSA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROBE Patient Reported Outcomes, Burdens and Experiences

PwH People with Haemophilia

PwMSH People with Moderate and Severe Haemophilia

PWV Pulse wave velocity

QoL Quality of life

ROM Range of movement

RM Repetition max

RPE Rate of perceived exertion

rpm Rotations per minute

r_s Spearman's rho correlation coefficient

SBP Systolic blood pressure

SD Standard deviation

SHL Standard half-life factor

SMM Skeletal muscle mass

SpO_2 Oxygen Saturation

SPSS Statistical Package for the Social Sciences

STROBE Strengthening the Reporting of Observational Studies in Epidemiology

TIIDM Type 2 diabetes mellitus

V Vertical

VM3 Vector magnitude

VO_2 Oxygen consumption

VO_{2max} Maximal volume of oxygen consumption

VPA Vigorous physical activity

vWF von Willebrand Factor

WC Waist Circumference

WFH World Federation of Hemophilia

WHO World Health Organisation

WHR Waist-to-Hip Ratio

WHtR Waist-to-Height Ratio

WMA World Medical Association

Chapter 1: Introduction

1.1 Haemophilia

1.1.1 Factor VIII and Factor IX

Vascular injury triggers haemostasis, which involves a series of complex biochemical and cellular processes that collectively aim to prevent excessive blood loss via the ultimate formation of a stable fibrin clot (Smith et al., 2015, O'Donnell et al., 2019). Thrombin is an enzyme which converts fibrinogen to fibrin and further activates platelets which adhere to the site of vascular injury, resulting in the stable cessation of bleeding (O'Donnell et al., 2019). Factor VIII (FVIII) and Factor IX (FIX) are two coagulation proteins activated in the plasma during haemostasis which contribute to thrombin generation. Together, activated FVIII and FIX form the intrinsic tenase complex, which accelerates the activation of Factor X, which along with its activated cofactor V, amplifies thrombin generation (Figure 1.1) (Smith et al., 2015, O'Donnell et al., 2019, Rehill et al., 2021). This amplification and consolidation of activated Factor X by the intrinsic tenase complex is integral to progress and sustain haemostasis to completion, resulting in the stable formation of a fibrin clot (Bolton-Maggs and Pasi, 2003, O'Donnell et al., 2019). The majority of FVIII circulates in the plasma bound to another coagulation protein called von Willebrand Factor (vWF) (Pipe et al., 2016).

Figure 1.1: "An integrated model of physiological coagulation"

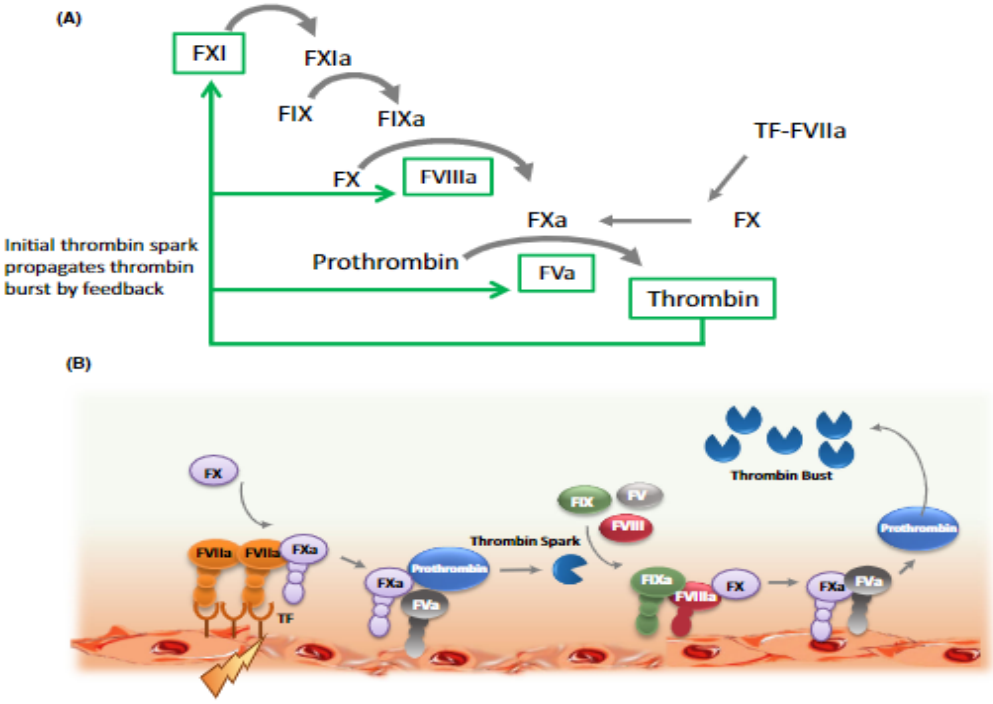


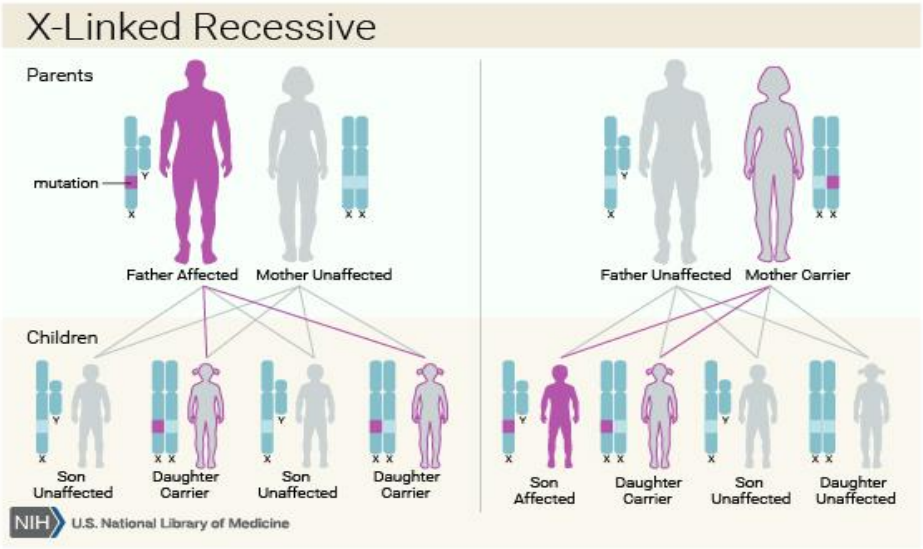
Fig 2. An integrated model of physiological coagulation. Evidence suggests that tissue factor (TF) exposure constitutes the principal trigger of physiological haemostasis *in vivo*. The TF:FVIIa complex is then able to active FX to FXa. In combination with its cofactor FVa, FXa is then able to convert prothrombin into thrombin. Critically, the small thrombin spark generated by initial TF exposure is then able to back activate FXI to FXIa, FVIII to FVIIIa and FV to FVa (illustrated by green lines). The net effect of this positive feedback loop amplification is that a secondary large amount of thrombin is generated. (B) Representation of sequential activation of clotting factors following physiological activation of haemostasis triggered by exposure of subendothelial tissue factor.

Source: O'Donnell et al. (2019)

1.1.2 Haemophilia A and Haemophilia B

Haemophilia A (HA) and Haemophilia B (HB) are inherited bleeding disorders caused by a deficiency of procoagulant FVIII or FIX, respectively. A deficiency of either factor ultimately impairs thrombin generation and results in an abnormal bleeding tendency in affected individuals (Mannucci and Tuddenham, 2001). The genes for FVIII and FIX lie on the 'X' chromosome. Although approximately 30% of cases arise from a spontaneous genetic mutation with no family history of haemophilia, the mode of inheritance in typical cases is considered to be X-linked recessive (Figure 1.2) (Mannucci and Tuddenham, 2001). Consequently, the typical clinical manifestation of haemophilia predominantly affects males who inherit an affected maternal 'X' chromosome (Mannucci and Tuddenham, 2001, Srivastava et al., 2020), although abnormal bleeding has also been reported in female carriers of haemophilia (Noone et al., 2019, Lavin et al., 2019, van Galen et al., 2020).

Figure 1.2: Genetic inheritance of haemophilia



Source: MedlinePlus, National Library of Medicine

The characteristic clinical presentation of people with haemophilia (PwH) is the bleeding tendency, which is also referred to as the bleeding phenotype. The severity of an individual's bleeding phenotype typically correlates with the degree of clotting factor that is deficient (Srivastava et al., 2020). The severity of haemophilia is classified by the International Society of Thrombosis and Haemostasis as mild, moderate or severe haemophilia according to basal clotting factor levels (i.e. <1%, 1-5% or >5-<40% of normal clotting factor levels, respectively) (Blanchette et al., 2014). Whilst people with mild haemophilia have an abnormal bleeding tendency with significant trauma or surgery, people with moderate or severe haemophilia (PwMSH) are affected by spontaneous bleeding (i.e. without associated trauma) or bleeding after only minor trauma (Mannucci and Tuddenham, 2001, Srivastava et al., 2020). The severity of haemophilia is summarised in Table 1.1.

Table 1.1: The severity of haemophilia

Severity	Clotting factor level	Typical clinical manifestations
Severe	<1% or <.01 IU/mL	Spontaneous joint and muscle bleeding predominantly in the absence of identifiable haemostatic challenge; bleeding with minor trauma or surgery.
Moderate	1-5% or .01-.05 IU/mL	Occasional spontaneous bleeding; bleeding with minor trauma or surgery.
Mild	>5-<40% or >.05-<.40 IU/mL	Rare spontaneous bleeding; bleeding with major trauma or surgery.

Sources: Blanchette et al. (2014), Srivastava et al. (2020).

The sites of bleeding in severe haemophilia predominantly involve joints (i.e. 'haemarthrosis') and muscles, and may also involve internal organs (Mannucci and Tuddenham, 2001, Srivastava et al., 2020). Haemarthroses account for approximately 70-80% of bleeding events and are most common in hinged joints, such as the ankles, knees and elbows, but may also affect multiaxial joints, such as the shoulders, wrists and hips (Aronstam et al., 1979, Srivastava et al., 2020). Muscle bleeds predominantly affect deep muscular compartments, such as the iliopsoas, calf and forearm muscle complexes, accounting for approximately 10-20% of bleeding events (Srivastava et al., 2020). Bleeds may also affect mucous membranes of the mouth, nose and genitourinary tract. Life-threatening sites of bleeding may involve intracranial, neck, throat or gastrointestinal bleeding (Srivastava et al., 2020).

The global prevalence of haemophilia is estimated to affect approximately 1,125,000 males, including approximately 418,000 people with severe haemophilia (Iorio et al., 2019). Specifically, the prevalence of males with all severities of HA is 24.6 cases per 100,000, including 9.5 cases per 100,000 with severe HA. The prevalence of males with all severities of HB is 5.0 cases per 100,000, including 1.5 cases per 100,000 with severe HB.

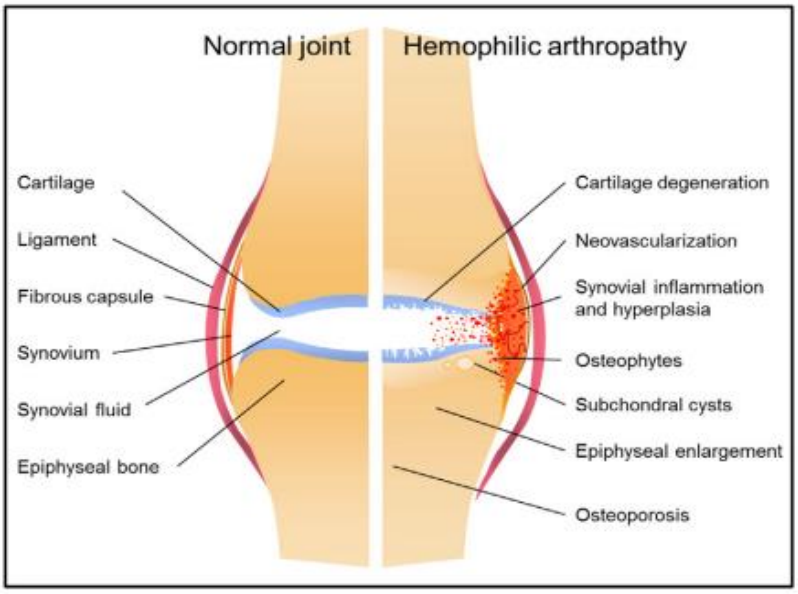
According to the World Federation of Hemophilia (WFH) Annual Global Survey reported in 2017 at the outset of this PhD project, there was a total of 330 PwMSH of all ages registered in Ireland. This figure consisted of 209 people with severe HA, 59 people with severe HB, 38 people with moderate HA, and 25 people with moderate HB (WFH, 2017). Of this, a total of 208 adult PwMSH ≥18 years (HA n= 151; HB n= 57) were registered at the National Coagulation Centre, St. James's Hospital Dublin. This centre is a designated European Haemophilia Comprehensive Care Centre for PwH in Ireland, in addition to Cork University Hospital and Children's Health Ireland at Crumlin. Comprehensive care centres offer a range of multi-disciplinary inpatient and outpatient services for patients and families, including specialist medical care, nursing, physiotherapy, social work, clinical psychology, and dentistry. There are four additional haemophilia treatment centres based in Donegal, Galway, Limerick and Waterford hospitals in Ireland.

1.1.3 Haemophilic arthropathy

Recurrent joint bleeding results in significant synovitis and osteochondral destruction, which ultimately leads to a chronic, degenerative joint disease known as 'haemophilic arthropathy' (Figure

1.3) (Raffini and Manno, 2007, Pulles et al., 2017). Synovitis increases the likelihood of more frequent haemarthroses (Hoyer, 1994). The most common sites affected by haemophilic arthropathy correlate with the most common sites of haemarthroses, which as mentioned, are the ankles, knees and elbows. The well-vascularised synovium of these joints and the mechanical stress they withstand due to frequent weight-bearing are suggested reasons for why they are more susceptible to bleeding (Pulles et al., 2017). Haemophilic arthropathy is associated with significant pain, swelling, reduced joint range of movement, musculoskeletal deformity and muscular atrophy, which may significantly impact physical function and overall quality of life in affected PwH (Mannucci and Tuddenham, 2001, Raffini and Manno, 2007). A joint which experiences three or more spontaneous bleeds within a consecutive six-month period is clinically defined as a 'target joint' (Blanchette et al., 2014).

Figure 1.3: Haemophilic arthropathy



Source: Pulles et al. (2017)

1.1.4 The evolution of haemophilia treatment

Prior to the advent of factor replacement therapy, haemophilia caused severe premature physical disability and death at a very young age (Hoyer, 1994). Deaths were commonly caused by surgery or traumatic haemorrhages, particularly intracranial haemorrhages (Franchini and Mannucci, 2012). Primitive treatment of bleeding events involved whole blood transfusions, however a large volume of blood was required to treat severe bleeding, and the risk of circulatory overload also presented challenges (Deaprtment of Health, 2002, Franchini and Mannucci, 2012). The ability to separate plasma from whole blood somewhat advanced the treatment of haemophilia via the episodic administration of fresh frozen plasma to treat acute bleeds. This, however, was also limited due to the volume of plasma required to treat severe bleeding, and to a lesser degree, circulatory overload (Hoyer, 1994). More specific and effective replacement therapy became available for severe HA in

the 1960s with infusions of a product called cryoprecipitate (Hoyer, 1994). Cryoprecipitate is derived from the 'sludge' portion of thawed frozen plasma and is rich in FVIII, although it does not contain FIX (Franchini and Mannucci, 2012). Bleeds could be effectively controlled using episodic treatment with cryoprecipitate, but long-term joint damage still resulted from recurring bleeds (Peters and Harris, 2018). The potency of cryoprecipitate was also quite variable, which presented challenges for estimating how much product would be sufficient to treat a bleed (Deapartment of Health, 2002).

The modern management of haemophilia treatment began in the 1970s with the advent of intravenously administered plasma-derived concentrates containing replacement coagulation factors, commonly referred to as clotting factor concentrates (CFCs) (Mannucci and Tuddenham, 2001, O'Mahony, 2020). Processes to manufacture FVIII and FIX from large pools of donated plasma enabled the ability to produce higher and more uniform concentrations of replacement clotting factors. For the first time, home treatment with CFCs was possible, which was a major advancement for the convenience of treatment and the potential treat a bleed as soon as possible, reducing the potential extent of joint damage (Mannucci and Tuddenham, 2001, O'Mahony, 2020). This resulted in considerable improvements in the quality of life of PwH. The 1970s also saw the beginning of comprehensive care centres for the treatment and management of haemophilia (O'Mahony, 2020).

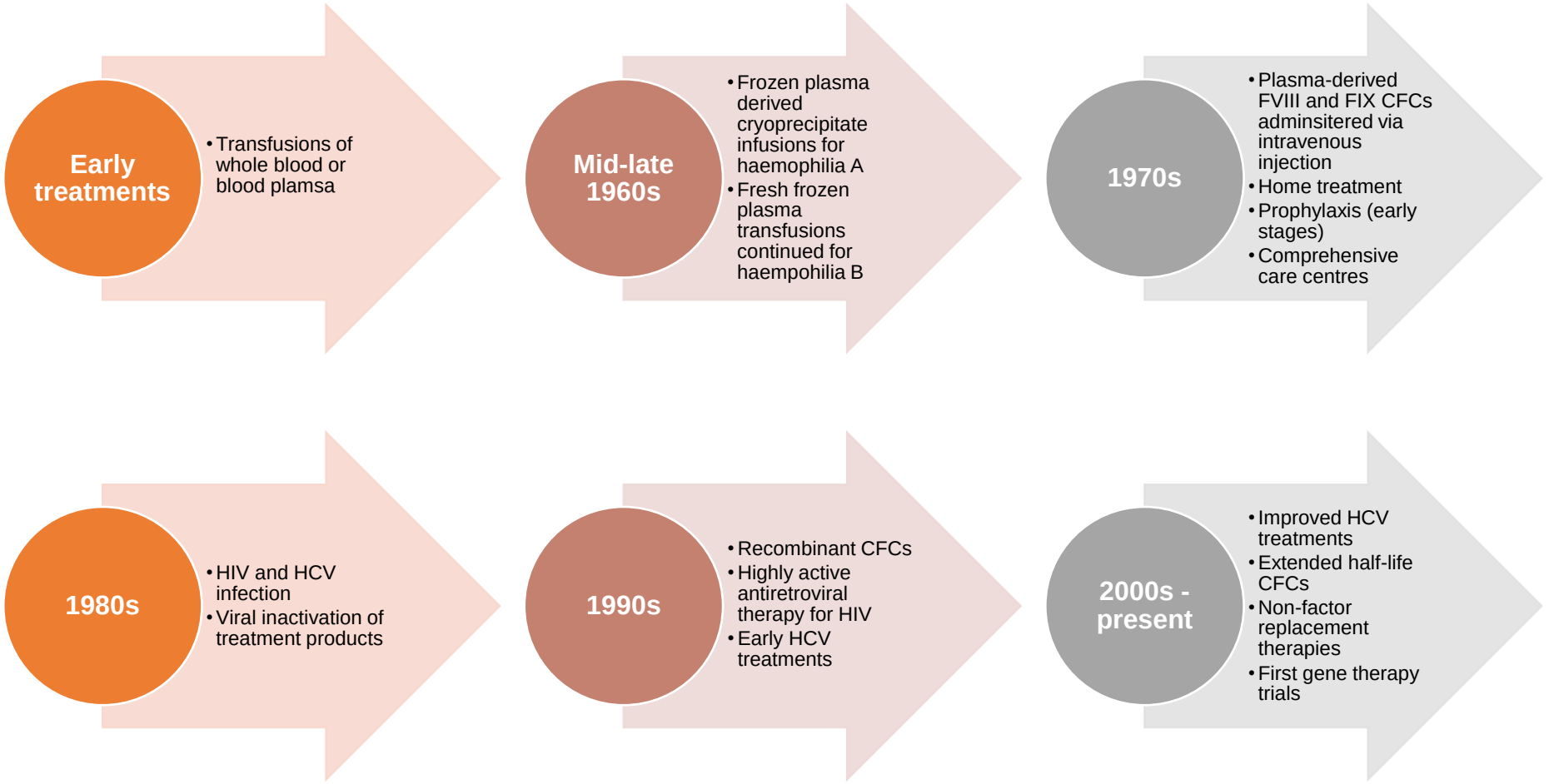
Replacement therapy is administered episodically (a.k.a. 'on demand') to treat an acute bleed, or according to a prophylactic treatment regimen (a.k.a. 'prophylaxis'). Prophylaxis strives to maintain clotting factor levels >1%, with the aim of preventing bleeds and maintaining or preventing further musculoskeletal damage (Mannucci and Tuddenham, 2001, Srivastava et al., 2020, Mancuso et al., 2021). The advent of effective CFC replacement therapy led to significant increases in the life expectancy of PwH. The median life expectancy of a person with severe haemophilia was 11.4 years from 1831-1920, which increased to the mid-twenties between 1921-1960, which thereafter increased to 56.8 years between 1961-1980 (Hoyer, 1994). This improved life expectancy, however, dramatically decreased from approximately 68 years between 1971-1980, to 49 years between 1981-1990 (Hoyer, 1994).

A number of incidents arose in the 1980s whereby CFCs from unscreened donors were found to be positive for a number of blood borne viruses, which predominantly included Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV). This unfortunately resulted in increased morbidity and mortality due to infections arising from viral exposure in approximately 60-70% of people with severe haemophilia in Western Europe and the United States, including potential co-infection (Mannucci and Tuddenham, 2001). Consequently, the previously increased life expectancy and relative improvements in quality of life of affected PwH were tragically diminished (Shapiro and Makris, 2019, Kempton et al., 2021). The impact of this period amongst the Irish haemophilia population is outlined in the Lindsay Tribunal report (Department of Health, 2002).

Thereafter, the safety of treatment improved with the advent of viral inactivation techniques of plasma-derived products, as well as genetically engineered recombinant CFCs (Mannucci and Tuddenham, 2001, Franchini and Mannucci, 2012). Screening for viral infections in the haemophilia population also became a standard of care. These improvements in treatment and care, as well as

improved treatments for HIV and the potential to eradicate HCV, have led to an increase in the life expectancy of the haemophilia population over recent decades, which now approaches that of the general population (Darby et al., 2007, Shapiro and Makris, 2019, Kempton et al., 2021, Alam et al., 2021). The use of prophylactic recombinant CFCs has been the standard of treatment for severe haemophilia in Ireland for the past few decades (Department of Health, 2002), although the treatment landscape of haemophilia has rapidly evolved in recent years with the advent of novel therapies (Mancuso et al., 2021). The evolution of the treatment of haemophilia is summarised in Figure 1.4.

Figure 1.4: A timeline of the evolution of haemophilia treatment



Sources: Hoyer (1994), Department of Health (2002), Franchini and Mannucci (2012), O'Mahony (2020).

1.1.5 Prophylaxis and novel therapies in the present day

Long-term prophylactic treatment with replacement CFCs commencing before or at the time of the first joint bleed is the standard of care for young children born with haemophilia (Srivastava et al., 2020, Mancuso et al., 2021, Collins et al., 2021). Long-term prophylaxis commencing as early as possible in life has been shown to be effective in preventing joint damage, target joints and life-threatening bleeds (Manco-Johnson et al., 2007, Oldenburg, 2015, Manco-Johnson et al., 2017b, Mancuso et al., 2021). Prophylactic treatment regimens may be classified as primary, secondary or tertiary prophylaxis, according to the age of commencement and the degree of haemophilic arthropathy present (Table 1.2) (Blanchette et al., 2014, Srivastava et al., 2020). The majority of adults with haemophilia who participated in this project were treated with secondary or tertiary prophylaxis.

Table 1.2: Types of prophylactic treatment regimens

Type of prophylaxis	Definition
Primary	"Regular continuous* replacement therapy started in the absence of documented joint disease, determined by physical examination and/or imaging studies, and before the second clinically evident joint bleed and before the age of 3 years."
Secondary	"Regular continuous* replacement therapy started after two or more joint bleeds, but before the onset of joint disease documented by physical examination and/or imaging studies (typically after 3 or more years of age)."
Tertiary	"Regular continuous* replacement therapy started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints" (typically applies to prophylaxis commenced in adulthood).

"*Continuous is defined as the intent to treat for 52 weeks per year and receiving a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year under consideration."

Source: Blanchette et al. (2014), Srivastava et al. (2020)

Prophylaxis is not without risk and limitations. Some people who are treated with replacement therapy (i.e. predominantly those not previously exposed to treatment) may develop anti-FVIII or anti-FIX neutralising antibodies, called inhibitors (Oldenburg, 2015, Mancuso et al., 2021). Incidence rates of inhibitor development range between 25-40%. Inhibitors are complex to treat, requiring alternative haemostatic therapies which bypass the inhibitory effect of these antibodies (Mannucci and Tuddenham, 2001, Oldenburg, 2015). The high cost of prophylaxis also presents difficulties for accessing treatment in countries with limited healthcare resources (Skinner, 2012, Oldenburg, 2015, Mancuso et al., 2021). Furthermore, adherence to treatment may impact the efficacy of prophylaxis, especially amongst individuals who require frequent doses of intravenous injections in order to achieve and maintain adequate haemostatic concentrations of FVIII and FIX (Oldenburg, 2015, Mancuso et al., 2021).

Whilst prophylaxis may prevent the extent of joint damage and delay its development, it does not appear to completely prevent arthropathy (Oldenburg, 2015, Mancuso et al., 2021). Despite early long-term prophylaxis, a subset of individuals appear to develop significant arthropathy despite a low bleeding rate (Gooding et al., 2021). Additionally, joint deterioration continues to progress in some individuals who have established arthropathy and who are treated with prophylaxis, despite a relatively low number of bleeds. This evidence suggests possible recurrent asymptomatic or 'sub-clinical' joint bleeding (Gooding et al., 2021).

Various types of prophylactic treatment products exist. Standard half-life factor (SHL) CFCs have a relatively short half-life (i.e. FVIII: 8–12 hours; FIX: 18–24 hours) and require more frequent injections per week (i.e. 3-4 injections per week for HA and 2-3 injections per week for HB), although newer products may be more refined requiring less frequent infusions (Mancuso et al., 2021). The objective of SHL prophylaxis is to convert a person with severe haemophilia to a bleeding phenotype similar to that of a moderate phenotype, by maintaining factor levels >1% at all times (Srivastava et al., 2020). This concept was based on the fact that people with moderate haemophilia experience less spontaneous bleeding and better preservation of musculoskeletal health. It has been increasingly recognised, however, that factor levels of 1-3% are insufficient to completely prevent bleeding in all PwH (Srivastava et al., 2020).

Over the last decade, extended half-life factor (EHL) CFCs have been developed. EHL products have a prolonged half-life, which is at least one to three times that of SHL products (Mancuso et al., 2021). This allows for less frequent infusions (i.e. every 3-5 days for HA and every 7, 10 or 14 days for HB) and better protection from bleeds, as a prolonged factor half-life in the system maintains factor levels above the spontaneous bleeding range for longer. FIX EHL products have a longer half-life than FVIII products (Srivastava et al., 2020, Mancuso et al., 2021). These products contribute to easier personalisation of treatment and also have the potential to improve treatment adherence due to less burdensome treatment regimens (Mancuso et al., 2021). The majority of people with severe HA and severe HB were treating with EHL products when data collection commenced for this project.

Since the beginning of this project, various novel therapies have also become available in Ireland. Non-factor replacement products, which are administered subcutaneously, have been developed for HA. These products are also suitable for PwH who develop inhibitors. Emicizumab is a humanised bispecific monoclonal antibody which improves haemostatic function by mimicking the co-factorial function of activated FVIII (Mancuso et al., 2021). It is the first licensed non-replacement therapy for people with HA with or without inhibitors. A significant proportion of people with severe HA in Ireland have switched to this type of treatment in recent years. The advantages of emicizumab include the subcutaneous mode of administration, its use for people with inhibitors, and the relatively lower frequency of treatment whilst maintaining low bleeding rates (i.e. every 7, 14 or 28 days) (Mancuso et al., 2021). Individuals on non-factor replacement therapy may, however, still require episodic replacement therapy for breakthrough bleeds, or in cases of surgical intervention (Mancuso et al., 2021). Lastly, several gene therapy clinical trials have commenced in recent years with a curative

aim to provide a protective endogenous steady state production of FVIII and FIX in the plasma (Mancuso et al., 2021). Early phases of FIX gene therapy trials have commenced in Ireland.

1.1.6 Phenotypic variability in haemophilia

Despite a reduction in bleeding tendency due to prophylaxis, inter-individual variation in bleeding phenotype exists in approximately 10-15% of people with severe haemophilia who present with a milder bleeding tendency despite factor levels <1% (van den Berg et al., 2007, Jayandharan and Srivastava, 2008, Rehill et al., 2021). Furthermore, factor levels do not predict the frequency or severity of bleeds in individuals who have a milder bleeding tendency and do not require frequent prophylaxis (Rehill et al., 2021). Some individuals will have a low number of annual bleeds, require less frequent treatment and will experience minimal arthropathy despite bleeds, whilst this may be the opposite for others (Jayandharan and Srivastava, 2008, Rehill et al., 2021). This suggests that other factors may influence bleeding phenotype, although the underlying cause of phenotypic heterogeneity is not clear (Rehill et al., 2021). Influencing factors may include genetic mutations, variation in haemostatic pathways, pharmacokinetics of treatment (i.e. drug absorption, distribution, metabolism and excretion), the age of the first bleeding event, the age at which prophylactic treatment was commenced, treatment regimen adherence, body composition and activity levels (van den Berg et al., 2007, Schrijvers et al., 2016, Franchini and Mannucci, 2017, Franchini and Mannucci, 2018, Rehill et al., 2021). Additionally, people with HB may present with a milder bleeding phenotype compared to people with HA (Franchini and Mannucci, 2018, Castaman and Matino, 2019). This phenotypic variation has led to a shift in the concept of optimising haemophilia treatment in the present day. In contrast to the original fixed dose prophylactic treatment prescription which adapted a ‘one-size-fits-all’ approach, personalised prophylactic treatment regimens are now considered to be superior, where feasible (Srivastava et al., 2020). Personalised prophylaxis encompasses an individual’s bleeding phenotype, joint health, pharmacokinetics, activity levels and lifestyle, and incorporates both patient and clinician perspectives (Srivastava et al., 2020).

1.1.7 The ageing population with haemophilia

The life expectancy of the global haemophilia population has increased over recent decades and now approaches that of the general population, particularly in nations with sufficient health resources (Mauser-Bunschoten et al., 2009, Boccalandro et al., 2018, Shapiro and Makris, 2019, Kempton et al., 2021). Consequently, an increase in common comorbidities which affect the general ageing population has been recognised amongst the ageing haemophilia population, in addition to haemophilia-specific comorbidities.

1.1.7.1 Musculoskeletal health, bone health and physical function

Chronic haemophilic arthropathy causes significant musculoskeletal morbidity in affected PwMSH due to reduced joint rage of movement, musculoskeletal deformity and muscular atrophy. This results in significant acute and chronic pain, physical disability, reduced mobility, muscular weakness, impaired balance and functional disability (Raffini and Manno, 2007). Older adults with haemophilia

who did not have optimal access to treatment in their youth may be particularly burdened with severe arthropathy (Hodroj et al., 2021). The frequent requirement for pharmacological analgesia may also contribute to increasing levels of chronic pain with age (Hodroj et al., 2021). PwMSH are also at an increased risk of osteoporosis and related fractures at all ages compared to the general population (Petkovic et al., 2022). This may be due to reduced activity levels, arthropathy, muscular atrophy, HCV, HIV and vitamin D deficiency. Furthermore, thrombin is suggested to play a role in bone remodelling, therefore FVIII or FIX deficiency may indirectly affect bone metabolism via reduced thrombin generation (Petkovic et al., 2022). Reduced physical fitness, increased muscular weakness, impaired balance, muscular atrophy, reduced bone mineral density, and a consequent increased risk of falls and associated injuries, are all features of physiological ageing in the general population (Chodzko-Zajko et al., 2009). Evidently, there is significant potential for physiological ageing to be accelerated in PwMSH due to chronic, debilitating haemophilic arthropathy and reduced bone mineral density.

1.1.7.2 Cardiometabolic risk and disease

The overall extent of cardiovascular disease and cardiometabolic risk in PwH compared to the general population is unclear. Elevated levels of Factor VIII and vWF are associated with an increased risk of arterial thrombosis, therefore it has been suggested that PwH may be protected against cardiovascular thrombotic events due to reduced thrombin generation potential (Kamphuisen and ten Cate, 2014). It has been additionally suggested that PwH may be protected from thrombus formation, but not atherosclerosis, which appears to be equally prevalent in PwH compared to the general population (Sartori et al., 2008, Zwiers et al., 2012, Hodroj et al., 2021). Conflicting reports of cardiometabolic mortality and comorbidity exist in the literature (Rizwan et al., 2015). Comparable rates of cardiovascular disease and atherosclerosis between PwH and the general population have been reported (Miesbach et al., 2009, Kamphuisen and ten Cate, 2014, Wang, 2016). A large study reported higher rates of both ischaemic and haemorrhagic stroke, coronary artery disease, myocardial infarction, hypertension (HTN), hyperlipidaemia (HLD) and arterial thrombosis in PwH compared to the general population, which also appeared to occur at younger ages in PwH (Pocoski et al., 2014). No significant reduction in arterial thrombosis-related mortality has also been reported in PwH compared to the general population (Biere-Rafi et al., 2010, Samuelson Bannow et al., 2019).

More specifically, ischaemic heart disease mortality was reported to be lower in PwH who did not have HIV (Darby et al., 2007, Tuinenburg et al., 2009, Samuelson Bannow et al., 2019). The literature may, therefore, be confounded by the presence of HIV or HCV in some PwH, both of which are associated with elevated cardiometabolic risk (Mostafa et al., 2010, Freiberg et al., 2013, Samuelson Bannow et al., 2019). PwH who have HIV may be at an especially increased risk of cardiometabolic disorders and events due to the long-term side effects associated with antiviral therapy. Side effects of therapy include HLD, insulin resistance (IR) and type 2 diabetes (TIIDM), as well as an increased risk of myocardial infarction and intracranial haemorrhage (Konkle et al., 2009, Fransen van de Putte et al., 2013).

Higher prevalence rates of HTN have been reported in PwH compared to the general population (Canaro et al., 2015, Berger et al., 2016, Humphries et al., 2016), although conflicting reports do also exist (Holme et al., 2016, Seaman et al., 2017, Wilding et al., 2018). HTN has also been reported in PwH as young as their twenties (Barnes et al., 2016). This is particularly concerning due to an increased risk of intracranial haemorrhage (Street et al., 2006, Mauser-Bunschoten et al., 2009, Fransen van de Putte et al., 2012a, Samuelson Bannow et al., 2019). Interestingly, increased levels of vascular remodelling in haemophilic joints have been associated with HTN in this population (Barnes et al., 2017). Similar to the general population, age and obesity are also risk factors for HTN in PwH (Holme et al., 2016, Samuelson Bannow et al., 2019). Lastly, it is not yet known if the use of prophylaxis will influence cardiovascular risk in amongst the haemophilia population (Shapiro and Makris, 2019).

1.1.7.3 Obesity

Obesity and being overweight are amongst the leading risk factors of all-cause mortality and chronic disease (Murray et al., 2020). The prevalence of being overweight or obese is notably increasing in PwH, similar to the general population (Wong et al., 2011). Importantly, an inverse association between body mass index (BMI) and joint range of movement is suggestive of deteriorating lower limb arthropathy with increased body weight (Soucie et al., 2004, Soucie et al., 2011). In light of the significant weight loss associated with older HCV treatments, affected PwH who have successfully eradicated HCV may, therefore, be at an increased risk of unfavourable weight gain post-treatment (Mauser-Bunschoten et al., 2009). Furthermore, PwH who have HIV may be at an increased risk of central adiposity and obesity due to lipodystrophy which is a side effect of antiviral therapy (i.e. fat redistribution which varies in presentation, but may result in subcutaneous fat loss in the peripheries and increased adiposity centrally) (Carr, 2003, Grinspoon and Carr, 2005, Nduka et al., 2016).

1.1.7.4 Other comorbidities

Approximately 20-30% of PwH who were infected with HCV progress to liver cirrhosis within 15-20 years (i.e. late-stage scarring of the liver which impairs its function, which may ultimately progress to liver failure) (Hodroj et al., 2021). PwH who are living with HIV have also shown higher rates of progression to cirrhosis compared to those who have been affected by HCV alone. This may be due to increased HCV replication and hepatic inflammation caused by HIV, which has been associated with accelerated cirrhotic progression and liver failure (Aronsohn and Reau, 2009, Hodroj et al., 2021).

Chronic kidney disease is another common comorbidity in older PwH. Hospitalisation and mortality due to renal disease is up to 50-fold higher in PwH compared to the general population (Soucie et al., 2000, Kulkarni et al., 2003, Franchini and Mannucci, 2010). Factors which may contribute include frequent haematuria, HIV, HCV, nephrotoxic antiviral therapy, HTN and the frequent requirement for analgesia (Shapiro and Makris, 2019, Hodroj et al., 2021).

Due to the increase in life expectancy in recent decades, the risk of malignancy from cancers that are common in the general ageing population, such as prostate, colon and lung, are reported to be similar in the haemophilia population (Shapiro and Makris, 2019, Hodroj et al., 2021). Haemophilia itself however, is associated with a higher risk of viral-infection related malignancies such as HCV-associated hepatocellular carcinoma and HIV-related blood malignancies such as non-Hodgkin's lymphoma (Shapiro and Makris, 2019, Hodroj et al., 2021).

1.1.7.5 Mortality

A recent systematic review identified that all-cause mortality in PwH across North America and Europe has declined over recent decades and appears to be approaching that of the general population (Alam et al., 2021). Higher mortality amongst PwMSH compared to those with mild haemophilia was also demonstrated. Before the year 2000, HIV accounted for 31.2% of deaths followed by haemorrhage (26.0%), cardiovascular disease (18.2%), liver disease (9.0%) and cancer (including hepatocellular carcinoma) (8.9%) (Alam et al., 2021). After the year 2000, deaths due to HIV were fewer (13.9%). The proportion of deaths due to haemorrhage remained relatively similar (31.7%), but was the leading cause of death in both developed and developing nations. Risk factors for haemorrhage in PwH include age, HTN, severity of haemophilia and the presence of inhibitors (Nuss et al., 2001). Other causes of mortality included liver disease (14.3%), cancer (including hepatocellular carcinoma) (12.8%) and cardiovascular disease (12.5%) (Alam et al., 2021).

1.2 Physical activity

1.2.1 Definition of physical activity and intensity

Physical activity (PA) is defined in this thesis as "any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase in caloric requirements over resting energy expenditure," and should not be confused with the term "exercise" (Rochmis and Blackburn, 1971, Caspersen et al., 1985, Riebe et al., 2018). In contrast, "exercise" is defined as a "type of physical activity consisting of planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness," which includes the genre of sport-related activity (Caspersen et al., 1985, Plasqui and Westerterp, 2007, Riebe et al., 2018). PA can be subdivided into various domains including occupational, leisure-time, household, personal care and transport associated PA (Plasqui and Westerterp, 2007, Bull et al., 2020). It is also defined by the type of PA involved, which includes aerobic activity, muscle strengthening activity, bone strengthening activity, balance activity and multicomponent activities (Piercy et al., 2018). Regular aerobic PA is strongly associated with higher levels of cardiorespiratory fitness (CRF), which is an independent risk factor for cardiovascular, respiratory and metabolic diseases, and cancer (Jensen et al., 2017, Knaeps et al., 2018, Riebe et al., 2018, Steell et al., 2019). Definitions of the types of PA are summarised in Table 1.3.

Table 1.3: Types of physical activity

Type of physical activity	Definition
Aerobic	Also called endurance or cardio activity. Involves exercising large muscles moving in a rhythmic manner for a sustained period. Causes the heart rate to increase and breathing to become more laboured. Examples include brisk walking, cycling, swimming and jogging.
Muscle strengthening	Includes resistance training and weight lifting. Causes the body's muscles to work or hold against an applied force or weight. Involves lifting relatively heavy objects multiple times to strengthen muscles. May also involve using elastic bands or body weight as resistance.
Bone strengthening	Also called weight-bearing activity. Involves activity that produces force on the bones to promote bone growth and strength. This force is commonly produced by impact with the ground. Can involve aerobic and muscle strengthening activities.
Balance activity	Improves the ability to resist forces within or outside of the body that cause falls while a person is stationary or moving. Strengthening the muscles of the back, abdomen, and legs also improves balance.
Multicomponent activity	Includes a combination of balance, muscle-strengthening, and aerobic physical activity. May include gait training, coordination, functional training, or recreational activities such as dancing, yoga, tai chi, gardening, and sports.

Source: Piercy et al. (2018)

PA is described in terms of weekly frequency (i.e. the number of days), intensity (i.e. the level of relative exertion), type (as per Table 1.3) and duration (i.e. the amount of time spent in PA). PA causes an increase in energy-expenditure above resting levels, which is dependent on intensity of PA, body size and body composition (Plasqui and Westerterp, 2007, Strath et al., 2013). PA-related energy expenditure is the most variable of the three components which make up total daily energy expenditure: Resting energy expenditure (60-75%); PA-related energy expenditure (15-30%); and the thermic effect of food (10%) (Katch et al., 2011, Strath et al., 2013).

The intensity of PA may be classified in terms of an absolute scale or a relative scale. The Physical Activity Guidelines Advisory Committee (PAGAC) describes absolute intensity as the absolute rate of energy expenditure needed to undertake any form of PA, which may be measured by the metabolic equivalent of a task (MET), kilocalories, kilojoules or volume of oxygen consumption (VO_2) (Strath et al., 2013, PAGAC, 2018, Riebe et al., 2018). Alternatively, relative intensity depends on individual levels of CRF and is measured using physiologic parameters, such as the percentage of maximal volume of oxygen consumption (VO_2max), heart rate reserve (HRR), maximal heart rate (HR_{max}) or the rate of perceived exertion (RPE) (Strath et al., 2013, PAGAC, 2018, Riebe et al., 2018). The various definitions of PA intensity are summarised in Table 1.4.

Table 1.4: Definitions of physical activity intensity

	Relative intensity			Absolute intensity	
Intensity	**VO_2max (%) HRR (%)**	**HRmax (%)**	**RPE**	**Intensity**	**METs**
Very light	<25	<30	<9	**Sedentary**	1-1.5
Light	25-44	30-49	9-10	**Light**	1.6-2.9
Moderate	45-59	50-69	11-12	**Moderate**	3.0-5.9
Hard	60-84	70-89	13-16	**Vigorous**	≥6.0-9.0
Very hard	≥85	≥90	≥16		
Maximal	100	100	20		
HRR method: Target HR = [(HRmax/peak − HRrest) × % intensity desired] + HRrest **HR method:** Target HR = HRmax/peak* × % intensity desired **VO_2 method:** Target VO_2 = VO_2max/peak − % intensity desired					

HR Heart rate **HRmax** Maximal heart rate **HRR** Heart Rate Reserve **HRrest** Resting Heart rate **METs** Metabolic Equivalent of a Task **RPE** Rate of Perceived Exertion **VO_2max** Maximal Volume of Oxygen Consumption

Source: Strath et al. (2013)

1.2.2 The benefits of physical activity

Physical inactivity is amongst the leading established risk factors for all-cause mortality and several chronic diseases, including cardiovascular disease, TIIDM, and certain types of cancer (Piercy et al., 2018, Bull et al., 2020, Murray et al., 2020, Katzmarzyk et al., 2022). The numerous health benefits of PA are summarised in Table 1.5.

Table 1.5: The health benefits of regular physical activity

Benefits of physical activity for adults and older adults
Lower risk of all-cause mortality
Lower risk of cardiovascular mortality
Lower risk of cardiovascular disease
Lower risk of hypertension
Lower risk of type 2 diabetes
Lower risk of hyperlipidaemia
Lower risk of bladder cancer
Lower risk of breast cancer
Lower risk of colon cancer
Lower risk of endometrial cancer
Lower risk of oesophageal cancer
Lower risk of kidney cancer
Lower risk of lung cancer
Lower risk of stomach cancer
Improved cognition
Reduced risk of dementia
Improved quality of life
Reduced anxiety and depression
Improved sleep
Weight loss (with reduced caloric intake)
Reduced risk of weight gain or re-gain after loss
Improved bone health
Improved physical function
Lower risk of falls and falls-related injuries (older adults)

Source: Piercy et al. (2018)

PA guidelines suggest that adults should undertake 150-300 minutes of moderate intensity aerobic activity, or 75-150 minutes of vigorous intensity aerobic activity, or an equivalent combination, every week (Piercy et al., 2018, Bull et al., 2020). A wealth of evidence demonstrates that regular PA achieved according to these guidelines is associated with numerous health benefits. A dose-response relationship exists between higher volumes and intensity of PA with the magnitude of health benefits which may be acquired (Piercy et al., 2018, Bull et al., 2020). Guidelines further recommend that adults should do muscle strengthening activities targeting all major muscle groups of the body on two or more days per week. Older adults should also incorporate multicomponent activities that include balance, aerobic and strengthening activities. Over time, PA gets easier as the body adapts to performing specific types of activity. Individuals are therefore encouraged to progress the difficulty of PA as they become fitter, by increasing the frequency, intensity or duration of PA (Piercy et al.,

2018). For the purpose of this PhD, the emphasis is placed on the PA guidelines in relation to aerobic PA only.

1.2.3 Physical activity and haemophilia

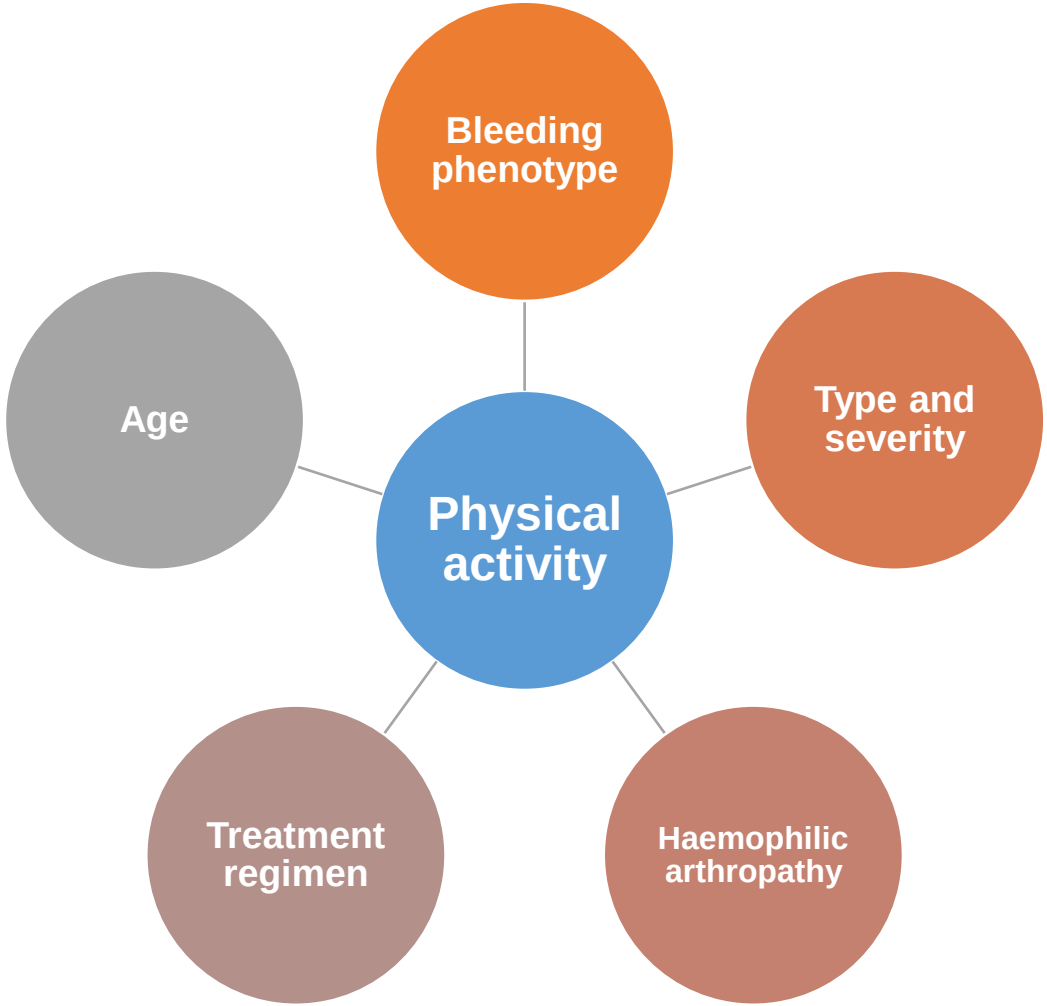
PwH may be exposed to an increased risk of bleeding with high impact, vigorous levels of PA, which may also occur due to potential trauma. Due to the increased risk of bleeding and potential joint injury when adequate treatment was not available, PwH were previously discouraged from partaking in strenuous PA (Weigel and Carlson, 1975, Von Mackensen, 2007). Encouragingly, with improved treatments over recent decades, the benefits of PA have been largely viewed to outweigh these risks. PA, generally of low impact and risk of collision, is now strongly recommended for PwH by the WFH due to the numerous potential health benefits associated with it (Negrier et al., 2013, Srivastava et al., 2020). A consensus, however, on the optimal volume, intensity and type of PA that is safe for individual PwH (i.e. that does not increase the risk of bleeding) is lacking. Types of PA have been risk stratified by the National Hemophilia Foundation according to the likelihood of impact or collision (Anderson and Forsyth, 2017). For instance, activities such as swimming and walking carry a low risk of impact or collision, whereas contact sports such as rugby and soccer carry a higher risk of impact or collision, and potential for serious or life-threatening bleeds. Estimations of the minimum and ideal factor levels required to participate in these risk stratified activity categories have also been proposed (Martin et al., 2020). The practical use of these guidelines may be relatively limited in the absence of information about factor levels in real time. These general guidelines, whilst a useful guide for PwH to participate in PA in a relatively safe manner, may not be suitable for all individuals due to the phenotypic variation demonstrated amongst PwH. The underlying relationship between PA and bleeding phenotype amongst PwH is ultimately not clear at present, specifically with regard to the safety of various types, intensities and volumes of PA.

A Cochrane review undertaken by Strike et al., (2016) systematically reviewed the available evidence on the safety and effectiveness of exercise for PwH. Although exercise was found to be beneficial for numerous physical outcomes, the authors importantly identified that adverse events or outcomes regarding bleeding frequency were not measured or reported in the included studies (Strike et al., 2016). Large heterogeneity also existed amongst the available literature with respect to study samples and exercise interventions. Small sample sizes and potential bias further limited findings. Although participants in some studies took prophylaxis prior to participating in exercise, the authors concluded that these results must be taken with caution in light of the limitations identified. Overall, the safety of exercise interventions, particularly amongst those with severe haemophilia, was unclear (Strike et al., 2016).

Bleeds and haemophilic arthropathy experienced by PwMSH may evidently impact PA participation. PwMSH may therefore be potentially exposed to an increased risk of acquiring a range of chronic diseases and accelerated physical deterioration with age, more so than the general population. The impact of treatment regimen, especially in younger PwH may also influence the potential for PA

participation. Based off this rationale, the proposal underpinning this thesis is presented in Figure 1.5. This also inspired the aim of the systematic review presented in the next section.

Figure 1.5: Proposal of clinical phenotypic factors which may impact physical activity in people with haemophilia



1.3 Systematic Review

A systematic review of physical activity in people with haemophilia and its relationship with bleeding phenotype and treatment regimen

Publication: Kennedy, M., O'Gorman, P., Monaghan, A., Lavin, M., O'Mahony, B., O'Connell, N. M., O' Donnell, J. S., Turecek, P. L., Gormley, J. & on behalf of the iPATH Study. 2021. A systematic review of physical activity in people with haemophilia and its relationship with bleeding phenotype and treatment regimen. Haemophilia, 27: 544-562.

1.3.1 Introduction

The improvement in treatment over recent decades has increased the life expectancy of PwH to be similar to that of the general population (Darby et al., 2007, Canaro et al., 2015). PwH were previously discouraged from being physically active due to the perceived increased risk of bleeding (Weigel and Carlson, 1975, Von Mackensen, 2007). The introduction of CFCs, however, has led to a change in attitudes towards PA (Negrier et al., 2013). PA and exercise (generally of low impact and risk) are now recommended for PwH. There has been some evidence to suggest it may reduce the risk of bleeds and improve joint integrity (Gomis et al., 2009, Srivastava et al., 2020).

Regular PA can reduce the risk of HTN and TIIDM, and contribute towards weight maintenance or loss (Piercy et al., 2018). These risk factors, including insufficient levels of PA, are amongst the leading causes of global mortality attributable to the development of non-communicable diseases, such as cardiovascular disease and certain types of cancer (Murray et al., 2020). An increase in cardiometabolic risk factors and disease, including HTN and obesity, are becoming more prevalent in PwH (Majumdar et al., 2010, Fransen van de Putte et al., 2012b, Canaro et al., 2015). The potential for PA to aid the treatment and management of these comorbidities is becoming more pertinent in the context of chronic health, particularly in the ageing population with haemophilia. PA guidelines suggest that adults should undertake 150-300 minutes of moderate intensity aerobic activity, or 75-150 minutes of vigorous intensity aerobic activity, or an equivalent combination, every week (Piercy et al., 2018, Bull et al., 2020).

Although the life expectancy of PwH has increased and some individuals may bleed less frequently than previously, the pain and disability of chronic haemophilic arthropathy still persists for many with moderate and severe haemophilia, which negatively affects physical function and quality of life (Raffini and Manno, 2007). Furthermore, the risk of bleeds and fear of joint damage have been identified as barriers to being active for some PwH (Baumann et al., 2017, Flaherty et al., 2018).

Despite having FVIII or FIX levels <.01 IU/mL, approximately 10-15% of people with severe haemophilia exhibit a milder spontaneous bleeding tendency and lower usage of CFC (Franchini and Mannucci, 2017). Further complicating phenotypic evaluation, the age of first joint bleed, pharmacokinetics of CFC clearance and the development of haemophilic arthropathy, have also been shown to vary (van den Berg et al., 2007, Franchini and Mannucci, 2017). Bleeding phenotype

may also be influenced by genetic factors, PA and obesity (Franchini and Mannucci, 2017). However, the true relationship between bleeds and PA volume (i.e. frequency, intensity, type and duration) is not fully understood.

An accurate understanding of the relationship between bleeds, PA and the influence of treatment regimen on this relationship would be beneficial to PwH, in order to identify safe and optimal levels of PA without increasing the risk of bleeds. The primary objective of this review was to determine levels of PA amongst PwH. Secondary objectives were to determine the currently available evidence of 1) the relationship between PA and bleeds, and 2) the influence of treatment regimen on this relationship.

1.3.2 Methods and materials

1.3.2.1 Protocol and registration

The protocol for this review was registered with the National Institute of Health Research, International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42018110106).

1.3.2.2 Search strategy

A search strategy including MeSH terminology related to “physical activity”; “exercise”; “h(a)emophilia”; “bleed”; “h(a)emorrhage”; and “h(a)emarthrosis” was created and tailored to each online database by a subject librarian (Appendix I). The online databases of EMBASE, Cochrane, MEDLINE Ovid, CINAHL and Web of Science were searched between February and March 2018. The same search was updated in December 2020. A manual search of reference lists of relevant articles was also conducted.

1.3.2.3 Eligibility criteria

Studies were selected using PECOS criteria (Table 1.6) as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Both children and adults with mild, moderate or severe FVIII or FIX deficiency were included. Outcomes included any measurement of PA and any reporting of bleeds, where available. Any information on treatment regimen was also recorded, where available. Interventional exercise or PA studies were not included, as it was considered that an intervention would influence PA levels, rather than capture habitual PA levels. Only full text publications available in English were considered. No date restrictions were placed on the search.

Table 1.6: PECOS criteria

	Inclusion	Exclusion
Participants	• Human • All ages and nationalities • Diagnosis of mild/ moderate/ severe FVIII/ FIX deficiency	• Animal studies • In vitro studies • Other rare bleeding disorders • von Willebrand Disease • Acquired haemophilia
Exposures	• +/- information on treatment regimen	• PA or exercise interventions
Comparators	• No comparators • Subgroup categories within study population (e.g. age or severity) • Control groups without haemophilia • PA guidelines	• Comparators not specified in inclusion criteria
Outcomes	• Any assessment of habitual PA (i.e. retrospective audit, observation, self-reported measures and objective measures). • +/- information on bleeds (i.e. annualised joint bleed rate, other bleed scores, self or documented report of number/ type/ cause of bleed, etc.)	• Outcomes not specified in inclusion criteria
Study Design	• Cross-sectional, cohort and case-control studies • Longitudinal/ prospective follow-up studies • Retrospective studies • Pilot studies	• Pre/post-interventional studies • Case reports • Systematic/ narrative reviews • Conference abstracts/ letters to the editor

1.3.2.4 Study selection and data extraction

Study screening and selection were performed by two independent reviewers (MK and POG). Conflicts were resolved via discussion with a third reviewer (AM), where necessary. Where full texts were unavailable, authors were contacted if correspondence details were available. Data were extracted using a standardised template pertaining to the PECOS criteria. Results were reported using a narrative synthesis.

1.3.2.5 Quality appraisal and risk of bias

Quality and transparency of reporting was analysed by one reviewer (MK) using the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) checklist and guidelines (Appendix II). STROBE is a standardised checklist of twenty-two items regarding the transparent

reporting of observational studies (Vandenbroucke et al., 2014). Four items were removed from the checklist, as they were not applicable across the majority of studies, resulting in the highest score achievable being 30. Removed items [6(b), 12(e), 14(c) and 16(c)] were related to reporting of participants in matched studies, sensitivity analysis, follow-up time of cohort studies and the translation of estimates of relative risk to absolute risk for a meaningful time period, respectively. A "Completeness of Reporting" (COR) score was calculated for each study. Higher scores indicated better transparency and quality of reporting. Mean ± standard deviation of COR score was calculated. The AXIS Critical Appraisal Tool for Cross-sectional Studies was assessed by two independent reviewers (MK and POG) (Downes et al., 2016) (Appendix III). Conflicts were resolved via discussion with a third independent reviewer (AM), where necessary. Risk of bias was analysed and reported using a narrative synthesis.

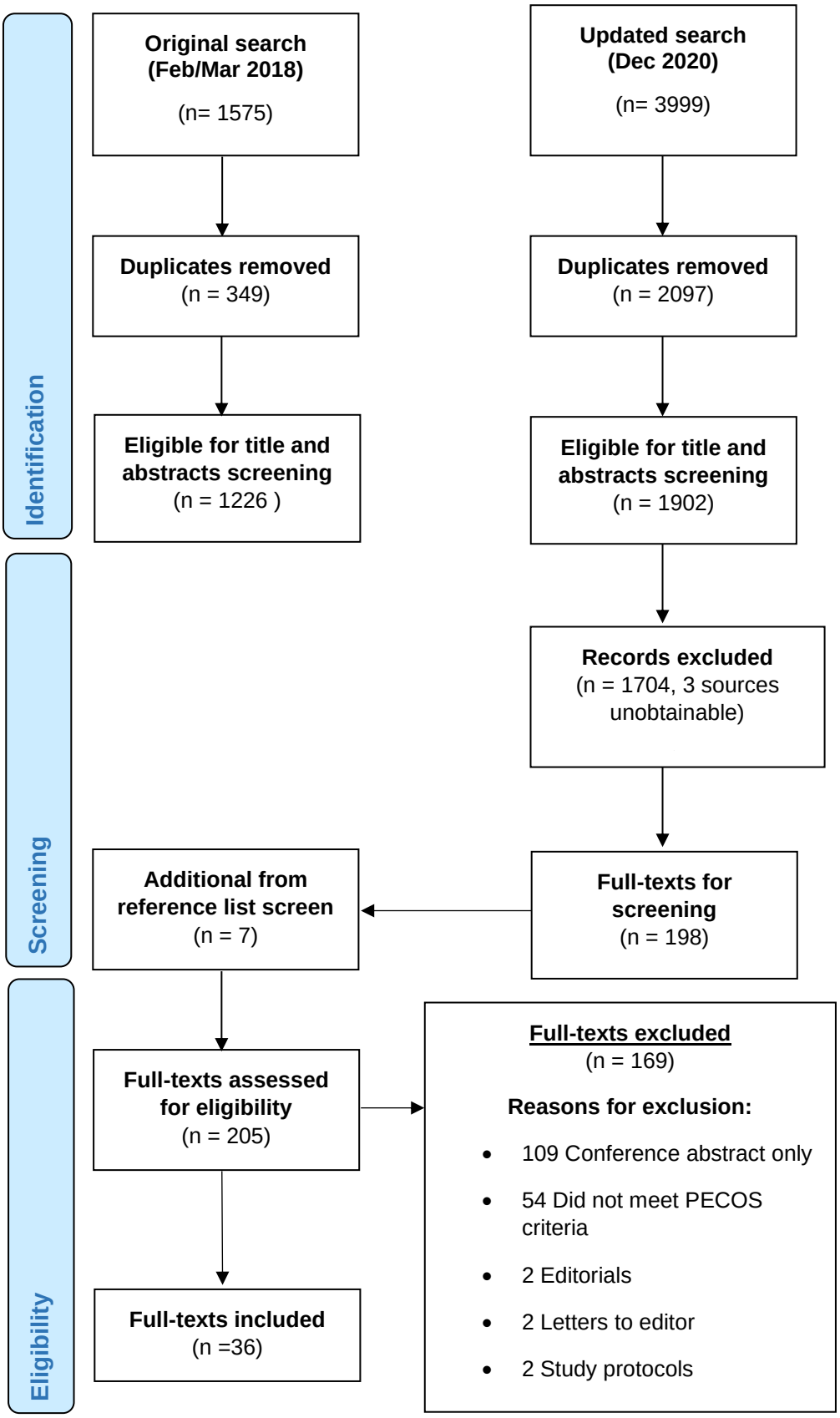
1.3.3 Results

1.3.3.1 Study selection

The online search identified a total of 1,902 sources (after duplicates). Seven additional articles were identified from the manual search (Heijnen et al., 2000, Tlacuilo-Parra et al., 2008, Köiter et al., 2009, Groen et al., 2011b, Broderick et al., 2013, Niu et al., 2014, von Mackensen et al., 2016). After the inclusion and exclusion criteria were applied, 36 articles were eligible (Janco et al., 1996, Heijnen et al., 2000, van der Net et al., 2006, Nazzaro et al., 2006, Fromme et al., 2007, Tlacuilo-Parra et al., 2008, Tiktinsky et al., 2009, Köiter et al., 2009, Ross et al., 2009, Sherlock et al., 2010, Khawaji et al., 2010, Buxbaum et al., 2010, Groen et al., 2011b, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Baumgardner et al., 2013, den Uijl et al., 2013, Broderick et al., 2013, Niu et al., 2014, McGee et al., 2015, von Mackensen et al., 2016, Cuesta-Barriuso et al., 2016, Bouskill et al., 2016, Carneiro et al., 2017, Baumann et al., 2017, Flaherty et al., 2018, Kempton et al., 2018, Pinto et al., 2018b, Pinto et al., 2018a, Versloot et al., 2019, Goto et al., 2019, Zanon et al., 2020, Timmer et al., 2020, Taylor et al., 2020, Berube et al., 2020).

A PRISMA flow diagram of the screening and selection process is provided in Figure 1.6.

Figure 1.6: PRISMA flow diagram



1.3.3.2 Quality appraisal and risk of bias

According to the STROBE analysis, the average COR score was 12.0 (±4.6) indicating low to moderate transparency and quality of reporting (Table 1.7). The AXIS tool appraisal identified moderate to high risks of bias amongst studies (Table 1.8). Considerable rates of selection bias were evident due to convenience sampling methods and a lack of specificity in defining target populations in 32 studies (Janco et al., 1996, Heijnen et al., 2000, van der Net et al., 2006, Nazzaro et al., 2006, Fromme et al., 2007, Tlacuilo-Parra et al., 2008, Tiktinsky et al., 2009, Ross et al., 2009, Sherlock et al., 2010, Khawaji et al., 2010, Buxbaum et al., 2010, Groen et al., 2011b, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Baumgardner et al., 2013, den Uijl et al., 2013, Broderick et al., 2013, Niu et al., 2014, McGee et al., 2015, von Mackensen et al., 2016, Cuesta-Barriuso et al., 2016, Bouskill et al., 2016, Carneiro et al., 2017, Baumann et al., 2017, Flaherty et al., 2018, Kempton et al., 2018, Versloot et al., 2019, Goto et al., 2019, Taylor et al., 2020, Timmer et al., 2020, Berube et al., 2020).

Inclusion and exclusion criteria were unclear in 21 studies (Janco et al., 1996, Heijnen et al., 2000, van der Net et al., 2006, Nazzaro et al., 2006, Fromme et al., 2007, Tlacuilo-Parra et al., 2008, Sherlock et al., 2010, Buxbaum et al., 2010, Groen et al., 2011b, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Baumgardner et al., 2013, den Uijl et al., 2013, Broderick et al., 2013, von Mackensen et al., 2016, Cuesta-Barriuso et al., 2016, Baumann et al., 2017, Flaherty et al., 2018, Versloot et al., 2019, Goto et al., 2019).

Non-response bias was also suspected for all except four studies (Heijnen et al., 2000, Ross et al., 2009, McGee et al., 2015, Zanon et al., 2020). Methods to address non-response were described by four studies (Pinto et al., 2018b, Versloot et al., 2019, Taylor et al., 2020, Baumgardner et al., 2013). Characteristics of non-responders were provided by four studies (Köiter et al., 2009, Baumgardner et al., 2013, Pinto et al., 2018b, Versloot et al., 2019).

Non-specific reporting of the validity or reliability of PA measurement tools (many which had not been validated in PwH), a lack of acknowledgement of potential confounders of PA, as well as the use of self-reported methods across the majority of studies raised concerns of measurement, social desirability and recall bias.

Potential selective reporting was suspected in 13 studies, as data were either not fully presented, or additional data which were not clearly described a priori in the methods were presented (Janco et al., 1996, Heijnen et al., 2000, van der Net et al., 2006, Fromme et al., 2007, Tlacuilo-Parra et al., 2008, Buxbaum et al., 2010, Khair et al., 2012, Broderick et al., 2013, von Mackensen et al., 2016, Kempton et al., 2018, Zanon et al., 2020, Taylor et al., 2020, Berube et al., 2020).

How missing data was managed was also unclear in 20 studies (Janco et al., 1996, Heijnen et al., 2000, van der Net et al., 2006, Nazzaro et al., 2006, Tlacuilo-Parra et al., 2008, Tiktinsky et al., 2009, Ross et al., 2009, Khawaji et al., 2010, Buxbaum et al., 2010, González et al., 2011, Khair et al., 2012, den Uijl et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Cuesta-Barriuso et al.,

2016, Pinto et al., 2018b, Versloot et al., 2019, Goto et al., 2019, Zanon et al., 2020, Taylor et al., 2020).

Table 1.7: STROBE analysis

		Janco et al. (1996)	Heijnen et al. (2000)	Van der Net et al. (2006)	Nazzaro et al. (2006)	Fromme et al. (2007)	Tlacuilo-Parra et al. (2008)	Tiktinsky et al. (2009)	Koiter et al. (2009)	Ross et al. (2009)	Sherlock et al. (2010)	Khawaji et al. (2010)	Buxbaum et al. (2010)	Groen et al. (2011)	Gonzalez et al. (2011)	Khair et al. (2012)	Broderick et al. (2012)	Baumgardner et al. (2013)	den Uijl et al. (2013)	Broderick et al. (2013)	Niu et al. (2014)	McGee et al. (2015)	Von Mackensen et al. (2016)	Cuesta-Barriuso et al. (2016)	Bouskill et al. (2016)	Carneiro et al. (2017)	Baumann et al. (2017)	Flaherty et al. (2018)	Kempton et al. (2018)	Pinto et al. (2018)	Pinto et al. (2018)	Versloot et al. (2019)	Goto et al. (2019)	Zanon et al. (2020)	Timmer et al. (2020)	Taylor et al. (2020)	Bérubé et al. (2020)
Title/abstract	1a	Y	N	Y	Y	N	Y	N	N	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Y	N
	1b	N	N	N	Y	Y	Y	Y	N	N	N	Y	N	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N
Introduction																																					
Background	2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Objectives	3	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Methods																																					
Study design	4	N	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	Y	N	N	N	Y	Y	N	Y	N	N	N	N	Y	Y	Y	N	N	Y	Y	N	N
Setting	5	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	N	N	Y	N	Y	N	N	N	N	Y	Y	Y	N	N	N	Y	N	N
Participants	6a	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	N	Y	N
Variables	7	N	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	Y	Y	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N
Data sources	8	N	N	N	N	N	N	Y	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Bias	9	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	N	Y	Y	N	N	N	N	N
Study size	10	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	N	Y	N	N	N	N	N	N
Quantitative	11	N	N	N	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Statistics	12a	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	N	N	N	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	N	N
	12b	N	N	N	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	Y	Y	*	N	N	N	Y	Y	Y	Y	Y	Y	Y
	12c	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	*	N	N	N	Y	N	N	N	Y	N	N
	12d	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	Y	*	N	N	N	Y	N	N	N	N	N	Y

'N'= No; **'Y'=** Yes; *** Not applicable**

Table 1.7: STROBE analysis (continued)

Results		Janco et al. (1996)	Heijnen et al. (2000)	Van der Net et al. (2006)	Nazzaro et al. (2006)	Fromme et al. (2007)	Tlacuilo-Parra et al. (2008)	Tiktinsky et al. (2009)	Koiter et al. (2009)	Ross et al. (2009)	Sherlock et al. (2010)	Khawaji et al. (2010)	Buxbaum et al. (2010)	Groen et al. (2011)	Gonzalez et al. (2011)	Khair et al. (2012)	Broderick et al. (2012)	Baumgardner et al. (2013)	den Uijl et al. (2013)	Broderick et al. (2013)	Niu et al. (2014)	McGee et al. (2015)	Von Mackensen et al. (2016)	Cuesta-Barriuso et al. (2016)	Bouskill et al. (2016)	Carneiro et al. (2017)	Baumann et al. (2017)	Flaherty et al. (2018)	Kempton et al. (2018)	Pinto et al. (2018)	Pinto et al. (2018)	Versloot et al. (2019)	Goto et al. (2019)	Zanon et al. (2020)	Timmer et al. (2020)	Taylor et al. (2020)	Bérubé et al. (2020)
Participants	13a	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	N	Y	Y	N	Y	Y	N	N	Y	N
	13b	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	*	N	N	N	Y	N	N	N	N	N	N	Y
	13c	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N
Descriptive data	14a	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	Y
	14b	N	N	N	N	Y	N	N	Y	N	Y	N	N	Y	N	N	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	N	Y	N	Y	N	N	N	Y	N	Y
Outcome data	15	N	N	N	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N
Main results	16a	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	N	Y	Y	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	Y	N	N	N
	16b	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	N	N	N	Y	Y	*	N	Y	Y	Y	Y	*	*	*	*	*	*	Y	*	Y	N	N	Y	Y	Y
Other analyses	17	N	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	N	Y	Y	N	Y	Y	Y	*	*	N	*	Y	Y	Y	N	Y	Y	Y
Discussion																																					
Key results	18	N	N	Y	N	N	Y	N	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	N	N	Y	N	N	N	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y
Limitations	19	N	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Interpretation	20	N	N	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Generalisability	21	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	N	N	N	N	N	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Other																																					
Funding	22	Y	N	N	Y	N	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	Y	N	N	Y	N	N	Y
COR Score		**4**	**4**	**10**	**9**	**3**	**8**	**13**	**14**	**15**	**10**	**13**	**10**	**12**	**14**	**12**	**23**	**17**	**7**	**11**	**17**	**18**	**13**	**12**	**13**	**17**	**8**	**8**	**13**	**17**	**24**	**13**	**11**	**8**	**15**	**16**	**15**
Mean COR		**12.0 ± 4.6 (3.0-24.0)†**																																			

'COR'= Completeness of Reporting; '**N'=** No; '**Y'=** Yes; *** Not applicable; † mean ± standard deviation (range)**

Table 1.8: AXIS critical appraisal

Introduction	Janco et al. (1996)	Heijnen et al. (2000)	Van der Net et al. (2006)	Nazzaro et al. (2006)	Fromme et al. (2007)	Tlacuilo-Parra et al. (2008)	Tiktinsky et al. (2009)	Koiter et al. (2009)	Ross et al. (2009)	Sherlock et al. (2010)	Khawaji et al. (2010)	Buxbaum et al. (2010)	Groen et al. (2011)	Gonzalez et al. (2011)	Khair et al. (2012)	Broderick et al. (2012)	Baumgardner et al. (2013)	den Uijl et al. (2013)	Broderick et al. (2013)	Niu et al. (2014)	McGee et al. (2015)	Von Mackensen et al. (2016)	Cuesta-Barriuso et al. (2016)	Bouskill et al. (2016)	Carneiro et al. (2017)	Baumann et al. (2017)	Flaherty et al. (2018)	Kempton et al. (2018)	Pinto et al. (2018)	Pinto et al. (2018)	Versloot et al. (2019)	Goto et al. (2019)	Zanon et al. (2020)	Timmer et al. (2020)	Taylor et al. (2020)	Bérubé et al. (2020)
Q1.	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y
Methods																																				
Q2.	Y	*	Y	Y	Y	Y	Y	Y	Y	Y	*	*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	*	Y	Y	Y	*
Q3.	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N
Q4.	N	Y	Y	N	N	N	Y	Y	Y	N	Y	N	N	N	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	N	Y	N	Y	Y
Q5.	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	N	N	N
Q6.	N	N	N	N	N	N	Y	Y	Y	N	Y	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	Y
Q7.	N	NA	N	N	N	N	N	N	NA	N	N	N	N	N	N	N	Y	N	N	N	NA	N	N	N	N	N	N	N	Y	N	Y	N	N	N	Y	N
Q8.	N	N	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	N	N
Q9.	N	N	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	N	Y	N	N
Q10.	N	N	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	NA	N	Y	NA	Y	Y	Y	Y	N	Y	Y
Q11.	N	N	Y	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	Y	Y
Results																																				
Q12.	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	N
Q13.	Y	N	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Q14.	N	NA	N	N	N	N	N	Y	NA	N	N	N	N	N	N	N	Y	N	N	N	NA	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N
Q15.	N	N	N	N	Y	N	N	Y	N	Y	N	N	Y	N	N	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	N	N	N	Y	N	Y
Q16.	N	N	N	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	N

*****Unable to Determine**; 'N'=** No; **'NA'=** Not applicable; **'Y'=** Yes. **Q1.** Were the aims/ objectives clear? **Q2.** Was the study design appropriate for the stated aim (s)? **Q3**. Was the sample size justified? **Q4.** Was the target/ reference population clearly defined? (Is it clear who the research was about?) **Q5.** Was the sample frame taken from an appropriate population base so that it closely represented the target/ reference population under investigation? **Q6.** Was the selection process likely to select subjects/ participants that were representative of the target/ reference population under investigation? **Q7.** Were measures undertaken to address and categorise non- responders? **Q8.** Were the risk factor and outcome variables measured appropriate to the aims of the study? **Q9.** Were the risk factor and outcome variables measured correctly using instruments / measurements that had been trialled, piloted or published previously? **Q10.** Is it clear what was used to determine statistical significance and/or precision estimates? (e.g. p-values, confidence intervals) **Q11.** Were the methods (including statistical methods) sufficiently described to enable them to be repeated? **Q12.** Were the basic data adequately described? **Q13.** Does the response rate raise concerns about non-response bias? **Q14.** If appropriate, was information about non- responders described? **Q15.** Were the results internally consistent? **Q16.** Were the results presented for all the analyses described in the methods?

Table 1.8: AXIS critical appraisal (continued)

	Janco et al. (1996)	Heijnen et al. (2000)	Van der Net et al. (2006)	Nazzaro et al. (2006)	Fromme et al. (2007)	Tlacuilo-Parra et al. (2008)	Tiktinsky et al. (2009)	Koiter et al. (2009)	Ross et al. (2009)	Sherlock et al. (2010)	Khawaji et al. (2010)	Buxbaum et al. (2010)	Groen et al. (2011)	Gonzalez et al. (2011)	Khair et al. (2012)	Broderick et al. (2012)	Baumgardner et al. (2013)	den Uijl et al. (2013)	Broderick et al. (2013)	Niu et al. (2014)	McGee et al. (2015)	Von Mackensen et al. (2016)	Cuesta-Barriuso et al. (2016)	Bouskill et al. (2016)	Carneiro et al. (2017)	Baumann et al. (2017)	Flaherty et al. (2018)	Kempton et al. (2018)	Pinto et al. (2018)	Pinto et al. (2018)	Versloot et al. (2019)	Goto et al. (2019)	Zanon et al. (2020)	Timmer et al. (2020)	Taylor et al. (2020)	Bérubé et al. (2020)
Discussion																																				
Q17.	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Q18.	N	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Other																																				
Q19.	Y	N	*	N	*	N	N	Y	*	N	N	Y	Y	N	N	Y	N	N	N	Y	N	Y	*	N	Y	Y	N	Y	N	N	Y	N	N	N	N	N
Q20a.	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Q20b.	Y	N	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	N	Y	Y

*****Unable to Determine**; 'N'=** No; **'NA'=** Not applicable; **'Y'=** Yes. **Q17.** Were the authors' discussions and conclusions justified by the results? **Q18.** Were the limitations of the study discussed? **Q19.** Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results? **Q20a.** Was ethical approval attained? **Q20b.** Was consent of participants attained?

1.3.3.3 Participants

Data on PA were available for 3,185 PwH. Approximately 1,361 children and adolescents (0-18 years) and 1,791 adults (18-85 years) were represented [numbers are estimated due to heterogeneity of age category boundaries and four studies (Köiter et al., 2009, Groen et al., 2011b, Kempton et al., 2018, Taylor et al., 2020) reported demographics of the total sample and not just those included in the PA analysis]. Mixed samples of children, adolescents and adults with haemophilia were included in 10 studies (Heijnen et al., 2000, Nazzaro et al., 2006, Fromme et al., 2007, Tiktinsky et al., 2009, Ross et al., 2009, Sherlock et al., 2010, Niu et al., 2014, Baumann et al., 2017, Pinto et al., 2018b, Zanon et al., 2020). Children and/or adolescents only were included in 15 studies (Janco et al., 1996, van der Net et al., 2006, Tlacuilo-Parra et al., 2008, Köiter et al., 2009, Buxbaum et al., 2010, Groen et al., 2011b, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Broderick et al., 2013, McGee et al., 2015, Cuesta-Barriuso et al., 2016, Bouskill et al., 2016, Carneiro et al., 2017, Berube et al., 2020). Adults only were included in 11 studies (Khawaji et al., 2010, Baumgardner et al., 2013, den Uijl et al., 2013, von Mackensen et al., 2016, Kempton et al., 2018, Flaherty et al., 2018, Versloot et al., 2019, Pinto et al., 2018a, Goto et al., 2019, Timmer et al., 2020, Taylor et al., 2020).

Approximately 1,701 and 887 participants had HA and HB, respectively [numbers are estimated numbers as four studies did not report on type of haemophilia (Nazzaro et al., 2006, Fromme et al., 2007, Sherlock et al., 2010, Groen et al., 2011b) and four others did not provide numbers of FVIII versus FIX deficiency for PA data (Heijnen et al., 2000, Buxbaum et al., 2010, den Uijl et al., 2013, Timmer et al., 2020). People with HA only were included in five studies (van der Net et al., 2006, Tlacuilo-Parra et al., 2008, González et al., 2011, Flaherty et al., 2018, Zanon et al., 2020). People with HB only were included in two studies (Niu et al., 2014, Baumann et al., 2017). Both types of haemophilia were included in 25 studies (Janco et al., 1996, Heijnen et al., 2000, Tiktinsky et al., 2009, Köiter et al., 2009, Ross et al., 2009, Khawaji et al., 2010, Buxbaum et al., 2010, Khair et al., 2012, Broderick et al., 2012, Baumgardner et al., 2013, den Uijl et al., 2013, Broderick et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Cuesta-Barriuso et al., 2016, Bouskill et al., 2016, Carneiro et al., 2017, Kempton et al., 2018, Pinto et al., 2018a, Pinto et al., 2018b, Versloot et al., 2019, Goto et al., 2019, Timmer et al., 2020, Taylor et al., 2020, Berube et al., 2020).

Approximately 732, 676 and 1,876 people with mild, moderate and severe haemophilia were represented, respectively [estimated numbers as three studies did not provide a breakdown of mild versus moderate (Niu et al., 2014, Bouskill et al., 2016, Timmer et al., 2020)]. Six studies focused on severe haemophilia only (van der Net et al., 2006, Tiktinsky et al., 2009, Khawaji et al., 2010, Versloot et al., 2019, Zanon et al., 2020, Berube et al., 2020). Five focused on moderate or severe haemophilia (Ross et al., 2009, Broderick et al., 2012, den Uijl et al., 2013, Broderick et al., 2013, Carneiro et al., 2017). The remaining 24 studies included all severities (Janco et al., 1996, Heijnen et al., 2000, Nazzaro et al., 2006, Fromme et al., 2007, Tlacuilo-Parra et al., 2008, Köiter et al., 2009, Sherlock et al., 2010, Buxbaum et al., 2010, Groen et al., 2011b, González et al., 2011, Khair et al., 2012, Baumgardner et al., 2013, Niu et al., 2014, McGee et al., 2015, von Mackensen et al., 2016,

Cuesta-Barriuso et al., 2016, Bouskill et al., 2016, Baumann et al., 2017, Flaherty et al., 2018, Kempton et al., 2018, Pinto et al., 2018b, Pinto et al., 2018a, Goto et al., 2019, Timmer et al., 2020).

1.3.3.4 Physical activity in people with haemophilia

Sample characteristics, PA outcome measures and main findings of all studies are presented in Table 1.9.

1.3.3.4.1 Self-report of physical activity

PA was assessed using various self-reported methods including diaries, surveys, non-specific questionnaires and interviews amongst 11 studies (Janco et al., 1996, van der Net et al., 2006, Nazzaro et al., 2006, Tlacuilo-Parra et al., 2008, Ross et al., 2009, Broderick et al., 2012, Baumann et al., 2017, Flaherty et al., 2018, Pinto et al., 2018b, Pinto et al., 2018a, Berube et al., 2020). Full breakdown of PA levels were not reported by four studies, although activity was categorised as "strenuous" (Janco et al., 1996) or by "risk" of PA (Ross et al., 2009, Broderick et al., 2012, Berube et al., 2020), and was investigated in relation to bleeds.

Lower levels of PA were found in children with mixed severities of HA compared to children without haemophilia in the study by Tlacuilo-Parra et al. (2008), whilst the study by van der Net et al. (2006) found variable levels of PA in children with severe HA compared to PA guidelines. Five remaining studies reported on PA in children and/or adults with haemophilia, however levels were not compared to normative data or PA guidelines (Nazzaro et al., 2006, Baumann et al., 2017, Flaherty et al., 2018, Pinto et al., 2018b, Pinto et al., 2018a).

1.3.3.4.2 Physical activity questionnaires

Specific questionnaires were used to assess PA by 15 studies. These included the Godin and Sheppard Questionnaire (Tiktinsky et al., 2009), the Framingham Physical Activity Index (Baumgardner et al., 2013), the Three Day Physical Activity Recall Questionnaire (Bouskill et al., 2016), the International Physical Activity Questionnaire (IPAQ) (Sherlock et al., 2010, den Uijl et al., 2013, Niu et al., 2014, Carneiro et al., 2017, Kempton et al., 2018, Versloot et al., 2019, Goto et al., 2019, Taylor et al., 2020), the Children's Physical Activity Questionnaire (CPAQ; parental proxy report) (Niu et al., 2014), the Modifiable Activity Questionnaire (MAQ) (Khawaji et al., 2010, Groen et al., 2011b, Broderick et al., 2013), and the EPIC Norfolk Physical Activity Questionnaire (Zanon et al., 2020).

The most commonly used questionnaire was the IPAQ. The reporting of results varied as different studies compared PA to guidelines (Niu et al., 2014), normative data (den Uijl et al., 2013) or a combination of both (Sherlock et al., 2010, Goto et al., 2019, Taylor et al., 2020). Using the IPAQ, Sherlock et al. (2010) reported that adults with haemophilia spent less time engaged in moderate-vigorous PA (MVPA) compared to normative data, whilst Goto et al. (2019) found their participants were less active compared to the sample assessed by Sherlock et al. (2010). Contrastingly, studies by Niu et al. (2014) and Taylor et al. (2020) found that the majority of adults with haemophilia met

PA guidelines. No differences in PA were found between adults and children with haemophilia and controls in the study by den Uijl et al. (2013).

Using the MAQ, Broderick et al. (2013) reported that children with haemophilia were less active than their peers without haemophilia, differing from the study by Groen et al. (2011), who reported higher levels of PA in youths with haemophilia compared to the general population. Neither majority in both studies achieved PA guidelines. The remaining eight studies did not compare PA against guidelines or normative data (Tiktinsky et al., 2009, Khawaji et al., 2010, Baumgardner et al., 2013, Niu et al., 2014, Carneiro et al., 2017, Kempton et al., 2018, Versloot et al., 2019, Zanon et al., 2020).

1.3.3.4.3 Objective measures of physical activity

Three studies used different accelerometer devices worn on the waist or hip for one week to assess PA in heterogeneous samples of children with haemophilia (Buxbaum et al., 2010, González et al., 2011, Bouskill et al., 2016). Two studies found children with haemophilia spent more time in moderate PA compared to controls (Buxbaum et al., 2010, González et al., 2011). The remaining study found the average minutes spent in MVPA were close to meeting PA guidelines of one hour per day (Bouskill et al., 2016).

One recent study assessed PA using an accelerometer over one week in adults with haemophilia (Timmer et al., 2020). A different method of classifying PA was used whereby PA behaviour was classified as movement behaviour. Participants were categorised according to type of PA regularly undertaken (i.e. 'sedentary', 'walkers' or 'bikers and runners,'). The majority of participants were categorised as sedentary (Timmer et al., 2020).

1.3.3.4.4 Participation in sport

Participation in sport was described by 16 studies (Heijnen et al., 2000, Fromme et al., 2007, Köiter et al., 2009, Ross et al., 2009, Sherlock et al., 2010, Khair et al., 2012, den Uijl et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Cuesta-Barriuso et al., 2016, Baumann et al., 2017, Pinto et al., 2018b, Versloot et al., 2019, Goto et al., 2019, Taylor et al., 2020, Zanon et al., 2020), in addition to three studies who described types of PA undertaken using the MAQ (Khawaji et al., 2010, Groen et al., 2011b, Broderick et al., 2013). Considerable levels of engagement in sport were evident across 10 studies (i.e. more than half of the total sample engaged) (Heijnen et al., 2000, Fromme et al., 2007, Köiter et al., 2009, Ross et al., 2009, Sherlock et al., 2010, Khair et al., 2012, den Uijl et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Versloot et al., 2019). A wide variety of sports (both high and low risk) were captured across all 19 studies (see Table 1.9).

Lower rates of engagement in sport were found in PwH compared to normative data in the study by den Uijl et al. (2013). Two other studies found PwH were as engaged in sport as controls were (Heijnen et al., 2000, Cuesta-Barriuso et al., 2016). Additionally, Versloot et al. (2019) found that the level of engagement in sport in adults with haemophilia was similar to their peers. Trends in reduced sports participation with age were also found by two studies (Pinto et al., 2018b, Goto et al., 2019).

Table 1.9: Study sample characteristics, physical activity outcome measures and main findings

Author and sample size	Age (y)	Type	Severity	PA outcome	Main findings
Janco et al. (1996) **n=** 96	4-17 (range)	Both	All	6 month daily checklist of PA i.e. any strenuous or out of school activity; time spent with friend for 30 mins not at school; house hold tasks.	Higher clotting factor levels reported higher levels of strenuous PA (P<0.04). When controlled for factor level, higher levels of strenuous activity had higher rates of spontaneous joint bleeding (P< 0.05) and higher rates of trauma-related soft tissue bleeding (P<0.03).
Heijnen et al. (2000) **n=** 293	<6->29 (range)	Both	All	Self-administered PA questionnaire.	Participated in 1+ sports: 74%; "Not active" = 26%; Sev: "Active" = 71% "Not active" =29%; "As active" as Dutch male population (survey in 1990/91- 32% 'not active', 45% were semi-active and 23% were active).
Van der Net et al. (2006) **n=** 13	6.6† (range 8-14.6)	FVIII	Sev	Self-report: Hrs of PA at home; school; extra-curricular sports; leisure time in 1 wk.	245 (133.2; range: 90–540)**†** mins/wk i.e. Between ±60% and ±180% of the Dutch PA guidelines (Moderate PA for at least 420 mins/wk, including twice a week vigorous sports activities.).
Nazzaro et al. (2006) **n=** 110	16.7† (range 13-21)	NS	All	Survey: 2 questions adapted from IPAQ on strenuous PA and 30 mins moderate PA over 1 wk.	Avoided or limited PA: 60%; Exercised as a preventative measure: 27%; Did not engage in regular strenuous/ moderate PA: 27%.
Fromme et al. (2007) **n=** 71 i.e. 44 youths, 27 adults	Youths 10.2±3† Adults 29.2±12.5†	NS	All	Self-administered questionnaire (everyday activities/ school sports/ leisure sports).	Regular participation in school sports: 79.6% youths; 37% adults did during school days (significant at P<0.05). Excused due to risk of injury: 33.3% adults; 13.6% youths *Youths:* 88.6% performed one or more leisure sports; *Adults:* 66.7% performed one or more leisure sports.
Tlacuilo-Parra et al. (2008) **n=** 62 x 2 (HG and CG)	HG 9.02±3.7† CG 9.3±3.7†	FVIII	All	Self-report on PA and inactivity (hrs/day spent in PA).	HG vs. CG: Grouped sedentary and low PA significant; Inactive: 77% vs. 51% Sedentary: 33% vs. 11% Low PA: 44% vs. 40%; (grouped- p=0.003, OR 3.24, 95% CI,1.36-7.79); Moderate PA: 23% vs. 38%; Intense PA: 0 vs. 11%.
Tiktinsky et al. (2009) **n=** 44	18±5† (range 12-25)	Both	Sev	G&SQ, 1 unit= Minimum 15 mins exercise outside PE and not associated with organized athletics.	Strenuous PA at least once/wk†: 56.8%; 5.0±6.9 units/wk; Moderate PA†: 4.5±6.9 units/wk; Mild PA†: 3.0±4.3 units/wk; G&SQ total score†: 77.9 ± 80.2 i.e. 9 METS (strenuous units/wk) + 5 METS (moderate units/wk) + 3 METS (mild units/wk).
Koiter et al. (2009) **n=** 99	12.6† (range 8-18)	Both	All	The Movement and Sport Questionnaire: 12 questions on participation in PE, sports and active lifestyle and list 3 sports (including duration and freq/wk).	1 sport minimum: All 99; 2+ sports: 80 (81%); Freq/wk: 5±3.2†; Soccer (42%); swimming (22%); tennis (21%); gymnastics (13%); cardio-fitness (13%).
Ross et al. (2009) **n=** 37	6-21 (range)	Both	Sev	Medical chart audit of athletic participation with telephone interview if data missing regarding PA type, prophylaxis use and injuries.	Athletic activities were organized and supervised by adults; occurred at least x2/7, minimum 30 mins PA. Athletic activities classified by likelihood of impact by NHF: High impact PA: 73%; Low impact PA: 27%.
Sherlock et al. (2010) **n=** 61	38† (range 16-63)	NS	All	IPAQ and questionnaire regarding participation in sport.	High PA: 46%; Moderate PA: 28%; Low PA: 16%; Sport: 51%; Moderate mins/wk†: 152.7 (±167.2); Vigorous mins/wk†: 141.1 (±145.6); Walking mins/wk†: 444 (±156.5); Sitting mins/wk†: 2262 (±1326.8); Half as much time in moderate and vigorous PA vs. EU average.
Khawaji et al. (2010) **n=** 30	30.5† (range 20-57)	Both	Sev	MAQ	Weight-bearing PA: 96.6 %; Vigorous PA: 56.6% (e.g. jogging, wood chopping, hunting); Non-weight-bearing PA: 60% (e.g. cycling, swimming, strength); Leisure walking: 63.3%; 4+ physical activities: 80%.

† mean±standard deviation; **‡** median±(interquartile range); **§** median±(range); **HG=** Haemophilia Group; **All=** Mild, moderate and severe; **Both=** FVIII and FIX deficiency; **CG=** Control Group; **/day**= Per day; **FVIII=** FVIII deficiency; **FIX=** FIX deficiency; **freq=** Frequency; **G&SQ=** Godin & Shepard Physical Activity Questionnaire; **hr(s)=** Hours; **IPAQ=** International Physical Activity Questionnaire; **MAQ=** Modifiable Activity Questionnaire; **METs=** Metabolic Equivalent of Task; **mins=** Minutes; **NHF=** National Haemophilia Foundation; **NS=** Not specified; **PA=** Physical Activity; **PE**= Physical education; **Sev=** Severe; **/wk=** Per week

Table 1.9: Study sample characteristics, physical activity outcome measures and main findings (continued)

Author and sample size	Age (y)	Type	Severity	PA outcome	Main findings	
Buxbaum et al. (2010) **n=** 62 i.e. HG (17); CG (44)	HG:13.71±2.1† CG:13.28±2†	Both (only FIX in severe group)	All	Biaxial accelerometer (Actitrac; IM systems, Baltimore, MD, USA) on waist for 7 consecutive days.	HG vs. CG PA (hrs/wk)†: Low: 70.24 (±7.1) vs.75.0 2(±6) [p= 0.010]; Moderate: 18.35 (±3.4) vs. 15.89 (±3.3) [p= 0.012]; High: 11.44 (±6.3) vs. 9.13 (±3.8) [p= 0.086]; Vigorous: 1.96 (±2.6) vs. 1.54 (±1.4) [p= 0.409]; Both spent >70%/day sedentary.	
Groen et al. (2011) **n=** 36	12.5±2.9† (range 8.2-17.4)	NS	All	MAQ compared with data from a previous study of the general Dutch population.	1+ activities at competitive level: 83%; Met guidelines (1-hr moderate PA/5-8 METs/day): 27.8% (vs. 21% in general population); Inactivity: 8% (vs. 12% in general population).	
González et al. (2011) **n=** 66 i.e. HG (41); CG (25)	HG:12.78(0.48)†SEM CG:15.9(0.18)†SEM	FVIII	All	Triaxial accelerometer (ActiGraph GT3X, Fort Walton Beach, FL, USA) on right hip for 7 consecutive days.	HG vs. CG PA (mins/day) †SEM: Sedentary: 356.78(16.6) vs. 479.41(19.62) [p< 0.001] Light: 450.24(18.68) vs. 479.41(19.62) [p < 0.001]; Moderate: 8.48(1.15) vs. 3.36(0.86) [p = 0.001]; Vigorous: 0.25(0.06) vs. 0.41(0.10) (not significant); MVPA: 8.74(1.19) vs. 3.77(0.88) [p = 0.001]; Total PA (counts/min):652.63(33.74) vs. 430.82(30.63) [p<0.001].	
Khair et al. (2012) **n=** 84	11.52±3.4† (range 5.83-17.86)	Both	All	Questionnaire regarding sporting activities (freq and duration of sport/wk)	Participation in sport: 90.5%; Number of sports per person: 4†; With friends: 80%; At school: 80%; Team/ club sports: 40%; Golf course/ gym: 50%; Total hrs/wk†: 4.9 **(**range 1-13); 1hr/wk: 2.6%; 2-5hrs/wk: 59.2%; 6-9hrs/wk: 35.5%; 10-13hrs/wk: 2.6%; Freq/wk: x1: 21.1% x2: 48.7% x3 27.6% x>3: 2.6%.	
Broderick et al. (2012) **n=** 104	9.5±4† (range 4-18)	Both	Mod/ Sev	Self-reported PA 3 days before a bleed, PA categorised by risk of collision using NHF criteria. PA in 8-hrs immediately before the bleed and two 8-hr windows at 24- and 48- hrs before the bleed.	Interviews conducted for 329 bleeds, there was exposure to: C2- Significant collisions might occur e.g. basketball: 30.6% of bleed windows- 24.8% 1st control windows, 21.4% 2nd; C3- Significant collisions inevitable e.g. wrestling: 7.0% of bleed windows- 3.4% 1st control windows, 4.6% 2nd.	
Baumgardner et al. (2013) **n=** 88	41 (31.9-52.4)‡	Both	All	Framingham PAI	PAI score: 30.8(27.7-35.8)‡; "Active" (score >38): 14%; "Sedentary" (score <28): 25%	
den Uijl et al. (2013) **n=** 199 i.e. HG (94); CG (105)	HG 25-27(20-33)‡ CG 24 (20-31)‡	Both	Mod/ Sev	IPAQ and a self-designed sports list specifying type of participation in sport during the preceding year.	IPAQ results (METs)‡: HG =3,276 (960-8,640) vs. CG= 3,023 (1,493-6,936) (p=0.26). Participation in sport: HG: Sev: 47(59%); Mod: 28(70%) vs. CG: 92(88%) (p<0.01) High risk sport: HG: Sev: 27(34%); Mod: 20(50%) vs. CG: 64(61%) (p<0.01).	
Broderick et al. (2013) **n=** 104 (66 prospective diaries)	9.5±4† (range 4-18)	Both	Mod/ Sev	MAQ (METs/ wk for past year) and a random 1-week prospective record of PA during year. PA categorised by risk of collision using NHF criteria.	Total leisure-time PA‡: 7.9 (4.6-13.0) hrs/wk; Vigorous PA (>6 METs)‡: 3.8 (1.6-6.4) hrs/wk; MVPA(>3METs)‡: 6.4 (3.7-10.0) hrs/wk; 1 sport minimum: 45% for all and 61% for boys >10 years; Inactivity/ day: 20.7 hrs (86.3%); C2 or C3 PA: 1.5 h (6.3%). Less than half met guidelines (43%) (less than children without haemophilia-57-67%).	
Niu et al. (2014) **n=** 122 (Adults- IPAQ (n=69): children CPAQ (n= 53)	5-14: 9.6±2.6† 15-64:35.2±15.5†	FIX	All	IPAQ and CPAQ (parental proxy report).	IPAQ: High PA: 62%; Moderate PA: 29%; Low PA: 9%; Walking‡: 210 mins; 79% achieved PA guidelines of 75-150 mins/wk MVPA.	CPAQ: No engagement in PA= 2 (n). 79% of parents reported their child participated in PA on at least 4 days/wk.

† mean±standard deviation; **‡** median±(interquartile range); **§** median±(range); **HG=** Haemophilia Group; **All=** Mild, moderate and severe; **Both=** FVIII and FIX deficiency; **C2=** Category 2 activity; **C3=** Category 3 activity; **CG=** Control Group; **CPAQ=** Children's Physical Activity Questionnaire; **/day=** Per day; **FVIII=** FVIII deficiency; **FIX=** FIX deficiency; **freq=** Frequency; **hr(s)=** Hours; **IPAQ=** International Physical Activity Questionnaire; **MAQ=** Modifiable Activity Questionnaire; **METs=** Metabolic Equivalent of Task; **mins=** Minutes; **Mod=** Moderate; **MVPA=** Moderate-vigorous physical activity; **NHF=** National Haemophilia Foundation; **NS**= Not specified; **PA=** Physical Activity; **PAI=** Physical Activity Index; **SEM=** Standard error of the mean; **Sev=** Severe; **/wk=** Per week

Table 1.9: Study sample characteristics, physical activity outcome measures and main findings (continued)

Author and sample size	Age (y)	Type	Severity	PA outcome	Main findings
McGee et al. (2015) **n=** 48	14.3±2.6† (range 10-18.8)	Both	All	Chart review of participation in organised sport (i.e. participating in sport at least x2/wk for 30-mins). PA categorised by risk of collision using adapted NHF criteria.	Sports participation 1 season minimum of organised sport: 62.5% (30) Basketball: 12/30; Hockey: 2/30 (against the advice of the haemophilia treatment team); Number of sports participated in: 1 (0–3)§.
von Mackensen et al. (2016) **n=** 50	35.12±14.7† (range 17–66)	Both	All	Questionnaire regarding sports (freq and duration/ wk).	Participation in sport: 64%; Number of sports per person: 2†; With friends: 81.3%; Team/ club sports: 37.5%; Golf course/ gym: 50%; Total hrs/wk: 3.71±1.7†- 1hr: 12.5%; 2-3hrs: 34.4%; 4hrs: 25%; 5-8hrs: 28.1%; Freq/wk: x1/7: 25% x2/7: 53.1% x3/7 18.8% x4/7: 3.1%.
Cuesta-Barriuso et al. (2016) **n=** 104 i.e. HG (53); CG (51)	HG 10.08±1.36† CG 9.78±1.22†	Both	All	Participation in sport.	Days practicing sports (days/wk)†(range): 1.29; HG: 1.81±1.75 (0-5); CG: 2.18±1.22 (0-5). No significant differences between groups; Sports played included swimming, cycling, tennis and football.
Bouskill et al. (2016) **n=** 66	11.52 ±3.99†	Both	All	Triaxial accelerometer (ActiGraph GT3X, ActiGraph Corp, Pensacota, FL, USA) on right hip for 7 consecutive days and 3DPAR.	ActiGraph data (mins/day) †: Sedentary: Sev: 633.4(± 121.3); Mild/mod: 327(±78.73); MVPA: Sev: 48(±20); Mild/ mod: 55(±18); 3DPAR (METs/day) †: Sev: 3.54(±2.17); Mild/ mod: 4.71(±2.86). Close to meeting guidelines of 1hr/day.
Carneiro et al. (2017) **n=** 100 i.e. BrG (50); CaG (50)	BrG 13±2.9† CaG 12.1±2.8†	Both	Mod/ Sev	IPAQ	IPAQ vigorous METs‡ [BrG (n-10) vs. CaG]: 480 (960) vs. 1200 (3120) (p= 0.0017). Overall activity BrG vs. CaG (n): High 18 vs. 28 (p= 0.0045); Moderate 13 vs. 16; Low 9 vs. 6.
Baumann et al. (2017) **n=** AG (299; 89/299 female); ChG (150; 29/ 150 female)	AG 29(18-70)§ ChG 10(0-18)§	FIX	All	Survey on participation in recreational activities accounting for severity and treatment regimen, intensity and duration of activities.	Most common current recreational activities: AG: Walking (44%), dancing (26%), fishing (19%), and bicycling (16%); ChG: Walking (49%), swimming (18%), bicycling (11%), jogging/running (11%), and martial arts (8%); *Intensity and mean/ median duration of PA provided in article.
Flaherty et al. (2018) **n=**14	48† (range 24-77)	FVIII	All	Semi-structured interviews in person or by phone.	-11 reported daily PA, 2 reported being mostly sedentary; 2 reported current PA reduced from normal/desired routine due to injury - Walking most common type of PA reported; 6 reported regular exercise, average 5 days/wk, 4 daily; Large variety including walking, running, fitness class, cycling, hiking, kayaking, etc.; 8 infrequently exercised.
Kempton et al. (2018) **n=** 339 (IPAQ completed)/381	34 (26.3, 47.2)‡	Both	All	IPAQ	166 (49.0%) reported PA in previous wk; Duration (mins/wk)‡: Walking: 60 (30, 240); Moderate PA: 90 (60, 180); Vigorous PA: 105 (60, 180); MET (mins/wk)‡: Walking: 346.5 (198.0, 660.0); Moderate PA: 360.0 (160.0, 600.0); Vigorous PA: 960.0 (360.0, 3360.0).
Pinto et al. (2018) **n=** 146 AG (106); CTG (21); CPrG (6-9y n= 11, 1-5y n=8)	AG 43.49 (13.89)† CTG 14.00 (2.39)† ChG:6-9y: 7.73 (1.01)† ; 1-5y: 3.38 (1.60)†	Both	All	PA questionnaire which collected information on PA and sports participation.	Regular participation (n): AG= 29 (27.4%), swimming (16), walking (5), cycling (3); CTG= 12 (57.1%), swimming (5), football (3), dance (2), gym (2); ChG 6-9y= 9 (81.8%), swimming (7), hockey (1), dance (1); ChG 1-5y= 4 (50.0%), swimming (4), football (1).
Pinto et al. (2018) **n=** 102	43 (18-74)§	Both	All	Questionnaire on either regular or occasional PA (freq and types of PA).	65 (63.7%) practiced PA, no detail on frequency and type provided in article.

† mean±standard deviation; **‡** median±(interquartile range); **§** median±(range); **HG=** Haemophilia Group; **AG=** Adult Group; **All=** Mild, moderate and severe; **Both=** FVIII and FIX deficiency; **BrG=** Brazilian Group; **CaG=** Canadian Group; **CG=** Control Group; **ChG=** Children/Caregivers of Children Group; **CTG=** Children/ Teenager Group; **/day=** Per day; **FVIII=** FVIII deficiency; **FIX=** FIX deficiency; **freq=** Frequency; **hr(s)=** Hours; **IPAQ=** International Physical Activity Questionnaire; **METs=** Metabolic Equivalent of Task; **mins=** Minutes; **Mod=** Moderate; **MVPA=** Moderate-vigorous physical activity; **NHF=** National Haemophilia Foundation; **PA=** Physical Activity; **Sev=** Severe; **/wk=** Per week; **y**= Years (age); **3DPAR=** 3-Day Physical Activity Recall Questionnaire

Table 1.9: Study sample characteristics, physical activity outcome measures and main findings (continued)

Author and sample size	Age (y)	Type	Severity	PA outcome	Main findings
Versloot et al. (2019) **n=** 144 i.e. DG (43); SG (28); DCG (46); SCG (27)	26 (23-30)‡	Both	Sev	IPAQ and a questionnaire listing 23 sports played during last 12 months. Freq. of sport performed/wk in May also asked. PA categorised by risk as per NHF classification.	High-risk sports: 59.2 % (DG 27.9%; SG 42.9%; p <0.05); IPAQ *DG vs. SG* (×1000 METs/wk)‡: 18-22y: 5.8 (1.1-15.1) vs. 3.5 (1.2-7.9); 23-29y: 5.0 (0.7-14.9) vs. 4.5 (1.3-12.0); 30-40y: 2.6 (1.1-12.1) vs. 1.8 (0.5-12.6); Number and freq of sports per group provided in article. Similar participation in sport between peers and PwH (raw data available upon request).
Goto et al. (2019) **n=** 106	40.8 (12.1)† (range 18-64)	Both	All	IPAQ and sports participation questionnaire	PA levels (MET-mins/wk)= 1501.8 (3413.0)†; 693.0‡ Significantly lower PA than Irish patients p<0.001 (Sherlock et al., (2010) had higher number of mild patients). Moderate PA (mins/wk)= 103.7 (372.1)†; <0.1‡; Vigorous PA (mins/wk)= 53.4 (209.6)†; <0.1‡; Walking (mins/wk)= 333.6 (1106.7)†; 122.5‡; Low PA n= 63 (59.4%); Moderate PA n= 29 (27.4%); High PA n=13 (12.3%). 0 mins/wk of vigorous PA, moderate PA and walking, n= 85 (80.2%), 81 (76.4%), and 32 (30.2%), respectively. Sports participation previous year n= 50 (47.2%).
Zanon et al. (2020) **n=** 40, ChG (12); AdoG (9); AG (19)	ChG= <12 AdoG= 12-18 AG= >18	FVIII	Sev	EPIC Norfolk PA Questionnaire	More PA/ sports participation noted in highly adherent patients on prophylaxis. A difference between adolescents and adults in type, freq, and impact of PA was noted (raw data NR). Type of sport by category of adherence (None-High): Hobby/leisure: None= 3 (15%); Min= 2 (10%); Low= 2 (10%); Med= 2 (10%); High= 11 (55%); Endurance sports: None= 3 (14.3%); Min= 2 (9.9%); Low= 2 (9.9%); Med=3 (14.3%); High= 11 (52.4%); Athletic sports: None= 2 (13.3%); Min= 2 (13.3%); Low= 1 (6.7%); Med=1 (6.7%); High= 9 (60%); Ball sports: None= 2 (16.7%); Min= NA; Low= 1 (8.3%); Med= 2 (16.7%); High= 7 (58.3%).
Timmer et al. (2020) **n=** 105	43 (30–54)‡	Both	All	Activ8 accelerometer carried in trouser pocket for 7 consecutive days.	Majority= Sedentary (n=60); Walkers (n=21); Bikers and runners (n=24) Sitting (hrs/day): 9.2 (7.4–10.6)‡ ; Standing (hrs/day): 2.8 (2.0–3.6)‡; Walking (hrs/day): 1.9 (1.4–2.5)‡; Biking (mins/day): 14.2 (5.8–28.7)‡; Running (mins/day): 0.6 (0.2–1.9)‡; Frequency of active bouts /day: 10.0 (7.1–12.7)‡; Length active bout (mins): 11.8 (10.6–14.3)‡.
Taylor et al. (2020) **n=** 72	44.5±15.5† (range 18-69)	Both	All (mod excluded from analysis)	IPAQ and questionnaire on types of activities involved in	High PA: Sev 17 (40%); Mild 15 (52%); Total 31 (43%); Moderate PA: Sev 19 (44%); Mild 9 (31%); Total 30 (42%); Low PA: Sev 7 (16%); Mild 5 (17%); Total 11 (15%) Total MET†(range): Sev 3770±3979 (219-20 739); Mild 4530±4457 (33-18 339); Total 4075±4164 (33-20 739); Vigorous and Moderate MET†(range): Sev 2567±3570 (0-18 660); Mild 3390±3682 (0-16 260); Total 2899±3613 (0-18 660); Self-reported achieved UK guidelines for activity: Sev 15/43 (35%); Mild 19/29 (65%); Total 34/72 (47%); 85% met UK PA guidelines (higher than general population).
Bérubé et al. (2020) **n=** 24	11.8±3.3† (range 6–18)	Both	Sev	Self-report of PA/wk for safe and high-risk PA in winter and summer- G&SQ wording used, parental proxy report taken for children <10y.	When those who practiced high risk vs. low risk PA were compared, those in the high risk category practiced more high-risk PA vs. those in the low risk category (p<0.05) (2.6 vs. 0.6 days/wk). No significant differences between categories with regards practice of lower risk PA.

† mean±standard deviation; **‡** median±(interquartile range); **§** median±(range); **HG=** Haemophilia Group; **AdoG=** Adolescent group; **AG=** Adult Group; **All=** Mild, moderate and severe; **Both=** FVIII and FIX deficiency; **ChG=** Children/Caregivers of Children Group; **/day=** Per day; **DG=** Dutch Group; **DCG=** Dutch Control Group; **FVIII=** FVIII deficiency; **FIX=** FIX deficiency; **freq=** Frequency; **G&SQ=** Godin & Shepard Physical Activity Questionnaire; **hr(s)=** Hours; **IPAQ=** International Physical Activity Questionnaire; **METs=** Metabolic Equivalent of Task; **Med**= Medium; **min**= Minimum; **mins=** Minutes; **Mod=** Moderate; **NA=** Not applicable; **NHF=** National Haemophilia Foundation; **NR=** Not reported; **PA=** Physical Activity; **SCG=** Swedish Control Group; **Sev=** Severe; **SG=** Swedish Group; **/wk=** Per week; **y**= Years (age)

1.3.3.5 Physical activity by severity of haemophilia

PA or sports participation were compared by severity of haemophilia in 15 studies (Table 1.10) (age range 4-69 years) (Janco et al., 1996, Heijnen et al., 2000, Köiter et al., 2009, Sherlock et al., 2010, Buxbaum et al., 2010, Groen et al., 2011b, Baumgardner et al., 2013, den Uijl et al., 2013, Niu et al., 2014, McGee et al., 2015, von Mackensen et al., 2016, Bouskill et al., 2016, Goto et al., 2019, Timmer et al., 2020, Taylor et al., 2020). People with non-severe haemophilia undertook more strenuous or higher levels of PA or sport in five studies (Janco et al., 1996, Sherlock et al., 2010, den Uijl et al., 2013, Niu et al., 2014, Taylor et al., 2020). Contrastingly, no differences were found between the severity of haemophilia and PA in 10 studies (Heijnen et al., 2000, Köiter et al., 2009, Buxbaum et al., 2010, Groen et al., 2011b, Baumgardner et al., 2013, Niu et al., 2014, McGee et al., 2015, Bouskill et al., 2016, Goto et al., 2019, Timmer et al., 2020). Greater amounts of PA or sports participation were reported by people with severe haemophilia compared to those with non-severe haemophilia in two studies (den Uijl et al., 2013, von Mackensen et al., 2016). Information on treatment regimen was incomplete in nine of these studies (Heijnen et al., 2000, Sherlock et al., 2010, Buxbaum et al., 2010, Baumgardner et al., 2013, den Uijl et al., 2013, Niu et al., 2014, McGee et al., 2015, Bouskill et al., 2016, Timmer et al., 2020). The remaining six studies included participants who were treated episodically or with prophylaxis (Janco et al., 1996, Köiter et al., 2009, Groen et al., 2011b, von Mackensen et al., 2016, Goto et al., 2019, Taylor et al., 2020).

Table 1.10: Physical activity and sports participation by haemophilia severity

Study	FVIII (n)	FIX (n)	Mild (n)	Mod (n)	Sev (n)	Treatment (n)	Findings
Janco et al. (1996)	86	10	21	20	55	OD: 96	Higher levels of clotting factor reported higher daily strenuous PA (p< 0.04).
Heijnen et al. (2000)	Both†	Both†	50	26	217	NR	Sports participation of those with mod/sev haemophilia were similar to those with mild (73% vs. 85%, respectively).
Koiter et al. (2009)	100	13	47	11	41	OD: 56; PR: 43	No significant differences in energy expenditure were found for haemophilia severity.
Sherlock et al. (2010)	NR	NR	25	6	30	NR	High PA levels were more commonly reported by people with mild/mod (64%) than sev (36%). Moderate PA levels were slightly more reported by people with sev (53%) than those with mild/mod (47%). Lower PA levels reported by people with sev (90%) compared with mild/mod (10%).
Buxbaum et al. (2010)	Both†	Both†	7	NA	9	OD: NR; PR: 9	No significant differences were found in time spent in higher PA between mild and sev groups (moderate PA, p= 0.81, high PA, p= 0.18, and vigorous PA, p= 0.29).
Groen et al. (2011)	NR	NR	19	7	21	OD:22; PR: 25	No statistically significant differences found in number of sports played by severity (p=0.09). More non-sev played football (p=0.04), more with sev swam (p=0.01). No differences between non-sev vs. sev for total PA hrs/wk (8.7 ± 3.8 vs. 8.6 ± 7.8), MET hrs/wk (54.9 ± 30.3 vs. 55.6 ± 53.4) or vigorous hrs/wk (6.2 ± 4.2 vs. 5.4 ± 6.3).
Baumgardner et al. (2013)	71	17	26	24	38	OD: NR; PR: 20	No relationship was identified between baseline factor VIII/IX levels and PA.
den Uijl et al. (2013)	105§	15§	NA	34	60	OD: NR; PR:90§	Patients with sev reported higher PA (median 4294 MET; IQR 1,554-10,480) than those with mod (median 2,484 MET; IQR 942-5,660). Participation in sport and high risk sport was higher in those with mod (70%, 50%) than those with sev (59%, 34%).
Niu et al. (2014)	NA	135	NR	NR	56	NR	Adults with mild/mod were more active than those with sev (p= 0.0413). No significant differences found for severity (p= 0.095) between those adults who did/ didn't achieve recommended PA guidelines. No statistically significant differences in PA by severity in children (p= 0.1639).
McGee et al. (2015)	31	17	13	9	26	OD: NR; PR: 32	No statistically significant differences were found for sports participation by severity.
Von Mackensen et al. (2016)	35	15	12	10	28	OD: 23; PR: 27	Significantly more with sev (78.6%) did sport vs. mild/mod (45.4%) (p< 0.017).
Bouskill et al. (2016)	56	10	(24)‡	(24)‡	42	OD:NR; PR: 47	Severity was not significantly associated with time spent in MVPA (p_{adj} = 0.32).
Goto et al. (2019)	88	18	7	19	78	OD: 37; PR: 70	No significant relationship found between PA and severity of haemophilia (p=0.783)
Timmer et al. (2020)	Both†	Both†	NR	NR	73	OD: NR; PR: 71	No significant differences identified in the proportion of people with sev haemophilia in clusters of PA type (p=0.28).
Taylor et al. (2020)	67	6	29	NA	44	OD: 42; PR: 31	High PA levels more commonly reported by people with mild (52%) vs. sev (40%). Those with sev reported significantly less vigorous/moderate METs (2567 SD 3570) than those with mild (3390 SD 3682) (p < .001). No statistically significant differences found between severity for total PA METs.

†Both FVIII and FIX deficiency assessed but breakdown of numbers not provided**. ‡** n represents 24 mixed mild/moderate group, breakdown of numbers not provided. **§** Overestimated n. **FVIII=** FVIII deficiency; **FIX**= FIX deficiency; **hr(s)=** Hour(s); **IQR=** Interquartile range; **METs=** Metabolic Equivalent of Task; **mins=** Minutes; **Mod=** Moderate; **MVPA=** Moderate-vigorous physical activity**; NA=** Not applicable; **NR=** Not reported; **OD=** On demand; **PA=** Physical Activity; **SD=** Standard deviation; **Sev=** Severe; **/wk=** Per week

1.3.3.6 Physical activity and bleeds

Data regarding PA and bleeds were reported by 21 studies which used various self-reported methods of PA and bleeds, including diaries, questionnaires, phone interviews and retrospective medical record audits (Janco et al., 1996, Fromme et al., 2007, Tiktinsky et al., 2009, Ross et al., 2009, Sherlock et al., 2010, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Baumgardner et al., 2013, den Uijl et al., 2013, Broderick et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Carneiro et al., 2017, Kempton et al., 2018, Versloot et al., 2019, Pinto et al., 2018b, Pinto et al., 2018a, Goto et al., 2019, Zanon et al., 2020, Berube et al., 2020). There was significant variation in participant demographics, the definition and assessment of bleeds, the assessment of PA and the reporting of treatment regimens.

The relationship between bleeds and PA was assessed by 14 studies (Table 1.11) (Janco et al., 1996, Fromme et al., 2007, Tiktinsky et al., 2009, Ross et al., 2009, Sherlock et al., 2010, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Broderick et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Versloot et al., 2019, Goto et al., 2019, Berube et al., 2020). Age varied amongst children and adults (4-66 years). Those with severe haemophilia only were assessed by four studies (Tiktinsky et al., 2009, Ross et al., 2009, Versloot et al., 2019, Berube et al., 2020). Two studies assessed those with moderate and severe haemophilia (Broderick et al., 2012, Broderick et al., 2013). The eight remaining studies assessed mild, moderate and severe haemophilia (Janco et al., 1996, Fromme et al., 2007, Sherlock et al., 2010, González et al., 2011, Khair et al., 2012, McGee et al., 2015, von Mackensen et al., 2016, Goto et al., 2019). Seven studies collected data on bleeds and PA, but did not carry out analysis between these variables (Baumgardner et al., 2013, den Uijl et al., 2013, Carneiro et al., 2017, Kempton et al., 2018, Pinto et al., 2018a, Pinto et al., 2018b, Zanon et al., 2020).

Two studies did not present data on treatment regimen (Fromme et al., 2007, Sherlock et al., 2010), whilst the remaining 12 studies provided some indication of whether participants were taking prophylaxis or treating episodically (Janco et al., 1996, Tiktinsky et al., 2009, Ross et al., 2009, González et al., 2011, Khair et al., 2012, Broderick et al., 2012, Broderick et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Versloot et al., 2019, Goto et al., 2019, Berube et al., 2020).

Studies by Fromme et al. (2007) and Sherlock et al. (2010) reported 17.6% and 55% of participants, respectively, experienced sports or exercise-related bleeds amongst heterogeneous samples of PwH. Additionally, Fromme et al. (2007) did not identify any association between bleeding rate and haemophilia severity. A higher prevalence of sport-induced bleeding (79.2%) was reported by Goto et al. (2019), although the association between PA and bleeds was not statistically significant. A significant association between bleeds and strenuous PA was found in children and youths with haemophilia, who were not treated with prophylaxis (including those with severe haemophilia), in the studies by Janco et al. (1996) and Tiktinsky et al. (2009). There was no significant association between high impact PA or sport with bleeding or injury in PwH who were treated episodically or with prophylaxis across heterogeneous samples of PwH amongst seven studies (Ross et al., 2009, Khair

et al., 2012, Broderick et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Versloot et al., 2019, Berube et al., 2020). Contrastingly, Gonzalez et al. (2011) identified that patients who suffered from a bleeding episode during the previous year undertook significantly more vigorous PA compared to those who did not suffer bleeding (including those on prophylaxis). Broderick et al. (2012), found that vigorous PA was transiently associated with a moderate increase in the relative risk of bleeding, but the absolute increase in the risk associated with PA was low.

1.3.3.7 Physical activity and treatment regimen

Where data was reported, approximately 849 participants were treated episodically and 1,617 were treated with prophylaxis. Details of treatment regimen for PA data were not reported by six studies (Heijnen et al., 2000, Fromme et al., 2007, Sherlock et al., 2010, den Uijl et al., 2013, Niu et al., 2014, Flaherty et al., 2018), and were not reported in full by eight studies (i.e. data were only available for those treated with prophylaxis and no alternative treatment, if any, was specified for the remainder of participants) (Tiktinsky et al., 2009, Buxbaum et al., 2010, Baumgardner et al., 2013, den Uijl et al., 2013, McGee et al., 2015, Bouskill et al., 2016, Timmer et al., 2020, Berube et al., 2020).

Six studies provided detail on the dosage or type of prophylaxis participants were using (i.e. primary, secondary, tertiary, long-term or short-term) or indicated the age at which treatment was commenced (van der Net et al., 2006, Khawaji et al., 2010, den Uijl et al., 2013, von Mackensen et al., 2016, Carneiro et al., 2017, Versloot et al., 2019). Prophylaxis was tailored to sport or PA in six studies (Nazzaro et al., 2006, Köiter et al., 2009, Sherlock et al., 2010, Khair et al., 2012, von Mackensen et al., 2016, Goto et al., 2019). Individuals with severe haemophilia and those taking routine treatment reported a negative impact of treatment burden on PA in a large survey by Baumann et al. (2017). This included changes to treatment dosing and timing before vigorous PA.

Children who had more access to treatment in the study by Carneiro et al. (2017) spent more time in higher intensity PA than those with limited access (Carneiro et al., 2017). Adults who treated with intermediate dose prophylaxis from the Netherlands demonstrated an age-related decline in sports participation (including high-risk sports), in contrast to adults who treated with higher dose prophylaxis from Sweden in the study by Versloot et al. (2019). Lastly, a recent study by Zanon et al. (2020) reported that people with severe HA who were more adherent to their prophylaxis regimen, engaged in more PA than those with lower adherence.

Table 1.11: Study sample characteristics and main findings of bleeds, physical activity and treatment regimen

Author Sample size	Age (y)	Type	Severity	Traumatic bleeds	Spontaneous bleeds	Other bleeds	Treatment	Bleeds and PA
Janco et al. (1996) **n= 96**	4-17	Both	All	Yes	Yes	NA	OD	Spontaneous joint bleeds ($p< 0.05$) and traumatic soft tissue bleeds ($p<0.03$) with strenuous PA when controlled for factor level.
Fromme et al. (2007) **n=71**	7-42	NS	All	NS	NS	Exercise-induced	NS	17.6% of bleeds were exercise-induced. 10.3% in youths, significantly less than adults (33.3%) ($p<0.05$). Sports like football, basketball and swimming were associated with bleeding complications. No statistically significant correlation between rate of bleeding complications and severity of haemophilia.
Tiktinsky et al. (2009) **n= 44**	12-25	Both	Sev	Yes	Yes	NA	PR excluded; Treatment NS	Traumatic bleeds significantly associated with strenuous PA ($p<0.01$). No significant differences between activity levels and mean number of bleeds.
Ross et al. (2009) **n= 37**	6-21	Both	Sev	NS	NS	Joint bleeds	PR	Not associated with high-impact PA (OR 0.32 (95% CI: 0.04-2.7, p=0.3)) Median acute joint bleeds for high impact PA: 0.05 (0-4); low impact PA: 0.5 (0-2).
Sherlock et al. (2010) **n= 61**	16-63	NS	All	NS	NS	Sports-related	NS	55% of participants has sports-associated bleeds. Bleeding episodes were reported in 7/8 patients with sev haemophilia.
Gonzalez et al. (2011) **n= 41**	8-18	FVIII	All	NS	NS	"a bleeding episode during the previous year"	OD & PR	Patients who suffered from a bleeding episode during the previous year vs. those who did not did significantly more vigorous PA. ($t39 = 3.41$, $p = 0.002$, $r = 0.28$).
Khair et al. (2012) **n= 84**	6-18	Both	All	NS	NS	Total, joint and sports-related bleeds in 6 months	OD & PR	Not associated with sedentary behaviour, sports participation, frequency or duration of sport.
Broderick et al. (2012) **n=104**	5-14	Both	Mod/ Sev	NS	NS	"An episode of bleeding requiring treatment with clotting factor"	OD & PR	Vigorous PA transiently associated with a moderate relative increase in risk of bleeding, thus absolute increase in risk associated with PA was low.
Broderick et al. (2013) **n= 104**	4-18	Both	Mod/ Sev	NS	NS	NS	OD & PR	Not associated with absolute or vigorous PA ($r_s = 0.05$ and 0.07, respectively).

All= Mild, moderate and severe; **Both=** FVIII and FIX deficiency**; Mod=** Moderate; **NA**= Not applicable; **NS=** Not specified; **OD=** On demand; **PA=** Physical activity; **PR=** Prophylaxis; **r**= Effect size; **r_s=** Spearman's rho; **Sev**= Severe; **y**= Years (age)

Table 1.11: Study sample characteristics and main findings of bleeds, physical activity and treatment regimen (continued)

Author Sample	Age (y)	Type	Severity	Traumatic bleeds	Spontaneous bleeds	Other bleeds	Treatment	Bleeds and PA
McGee et al. (2015) **n=48**	10-19	Both	All	NS	Excluded	New target joints/ injuries: soft tissue/ haemarthrosis/ muscle haemorrhage and head injury	Most on PR	Mean number of 'injuries' not associated with sports participation (p = 0.44). Two subjects (mild/mod haemophilia) who did sport developed target joints compared to those who did not participate in sport.
von Mackensen et al. (2016) **n= 50**	17-66	Both	All	NS	NS	Total, joint and sports-related bleeds in 6 months	OD & PR	Not associated with sedentary behaviour, sports participation, frequency or duration of sport.
Versloot et al. (2019) **n=71**	18-40	Both	Sev	NS	NS	Joint bleeds (annual and 5-year)	PR	Not associated with high-risk sports participation (r_s= −0.25, p = 0.27/ r_s = 0.08, p = 0.76) in either cohort.
Goto et al. (2019) **n=106**	18-64	Both	All	NS	NS	Bleeding caused by sports; Intra-articular bleeding	OD & PR	84 (79.2%) experienced bleeding while playing sports. No significant association between intra-articular bleeds during past 12 months and PA (r_s= −0.072, p= 0.466).
Bérubé et al. (2020) **n=24**	6-18	Both	Sev	NS	NS	Bleeds in past year	PR or immune tolerance therapy	No significant differences in number of bleeds episodes in past year between 'Risk Profile' and 'Safe Profile' categories (3.8(6.3) vs. 4.7(6.7), respectively).

All= Mild, moderate and severe; **Both=** FVIII and FIX deficiency**; Mod=** Moderate; **NS=** Not specified; **OD=** On demand; **PA=** Physical activity; **PR=** Prophylaxis; **r_s=** Spearman's rho; **Sev**= Severe; **y**= Years (age)

1.3.4 Discussion

The objective of this review was to determine levels of PA amongst PwH. Additional objectives were to determine the relationship between PA and bleeds, and to determine whether treatment regimen influences this relationship. Overall, it was observed that levels of PA and participation in sport varied markedly amongst the heterogeneous samples of PwH reported in the literature.

Across 15 studies, greater (Buxbaum et al., 2010, Groen et al., 2011b, González et al., 2011), similar (Heijnen et al., 2000, den Uijl et al., 2013, Niu et al., 2014, Cuesta-Barriuso et al., 2016, Bouskill et al., 2016, Versloot et al., 2019, Taylor et al., 2020), reduced (Tlacuilo-Parra et al., 2008, Sherlock et al., 2010, den Uijl et al., 2013, Broderick et al., 2013, Goto et al., 2019) or variable (van der Net et al., 2006) levels of more intensive PA or sports participation compared to normative data or PA guidelines were found. The remaining 21 studies did not compare PA to guidelines or normative data, limiting their interpretation (Janco et al., 1996, Nazzaro et al., 2006, Fromme et al., 2007, Tiktinsky et al., 2009, Köiter et al., 2009, Ross et al., 2009, Khawaji et al., 2010, Khair et al., 2012, Broderick et al., 2012, Baumgardner et al., 2013, McGee et al., 2015, von Mackensen et al., 2016, Carneiro et al., 2017, Baumann et al., 2017, Kempton et al., 2018, Flaherty et al., 2018, Pinto et al., 2018b, Pinto et al., 2018a, Zanon et al., 2020, Timmer et al., 2020, Berube et al., 2020). Within studies, increased PA in lower age groups was apparent, which may be due to improved treatments, access to treatments and better promotion of PA from a young age in recent decades (Tiktinsky et al., 2009, Sherlock et al., 2010, Baumgardner et al., 2013, Niu et al., 2014, von Mackensen et al., 2016, Bouskill et al., 2016, Baumann et al., 2017, Versloot et al., 2019). There were even considerable rates of participation in high risk sport in some youths (Ross et al., 2009, den Uijl et al., 2013, Versloot et al., 2019). Although an age-related decline in PA is also a common trend seen in the general population (Sallis, 2000), lower levels of PA amongst older adults with haemophilia may also be attributable to less promotion of PA when they were young due to less optimal treatments. Factors other than age that have been suggested to impact PA levels, including socioeconomic, cultural, environmental, personality and behavioural influences (Seefeldt et al., 2002), may also explain the variation in PA of PwH represented in this review.

A large variety of PA assessment methods were used with differing definitions of PA and inconsistent reporting of PA volume (frequency, intensity, type and duration). Many of the measurement tools used to assess PA have not been validated in PwH. The most commonly used PA questionnaire was the IPAQ, however its validity and reliability have been reported to be poor or inconclusive in the general population (Kim et al., 2013, Silsbury et al., 2015, Ryan et al., 2018). No studies have validated the IPAQ in adults with HA. Satisfactory reliability of the IPAQ was shown in adults with HB from the B-HERO-S study by Buckner et al. (2018), although construct validity was not assessed. Self-reported questionnaires, like the IPAQ and MAQ, are commonly chosen as convenient methods of PA assessment because they are time efficient and consider the various domains and dimensions of PA. However, they are largely susceptible to recall and social desirability bias and possess low levels of validity for the assessment of PA in the free-living setting (Strath et al., 2013). Objective

methods, including accelerometry, provide a more reliable assessment of frequency, intensity and duration of PA in the free-living setting without being overly burdensome on the participant (Strath et al., 2013). A small number of studies used accelerometers to assess habitual PA in children with haemophilia (Buxbaum et al., 2010, González et al., 2011, Bouskill et al., 2016) and one recent study was identified in adults (Timmer et al., 2020). Objective measurements of PA using accelerometry in children with haemophilia have been partially validated in mixed sample studies of children with chronic diseases, although various devices were examined, and one study assessed the validity of accelerometry for sedentary behaviour only (Takken et al., 2010, Walker et al., 2015, Timmer et al., 2018a). There is a need for more validation studies of objective measurements of PA in both children and adults with haemophilia, in addition to self-reported PA assessment tools. A combined approach of using self-reported and objective methods has the potential to provide the clearest, most feasible description of PA volume and type amongst PwH in this field of research.

The relationship between PA and bleeding rate remains inconclusive. This was due to heterogeneity amongst sample characteristics, methods and the definition of bleeds and PA. Bleeding in PwH may be spontaneous or trauma-related, but the differentiation between types of bleeding was difficult to determine from some studies who classified bleeds as 'joint bleeds', 'an episode of bleeding requiring treatment with clotting factor' or 'sports/exercise-related bleeds or injury'. A milder bleeding phenotype has been described in 10-15% of people with severe haemophilia, and in people with HB compared to HA (Franchini and Mannucci, 2017, Franchini and Mannucci, 2018). Despite the fact that type and severity of haemophilia appear to be significant genetic modifiers of bleeding phenotype, small sample sizes may have prevented studies comparing bleeds and PA in these subgroups. Fromme et al. (2007) were the only study to compare sports associated bleeds by haemophilia severity. However, this study involved a heterogeneous sample of PwH and was limited by a lack of information on treatment regimen. Further investigation is therefore warranted regarding the relationship between PA and bleeding, and the influence of treatment on this relationship.

The sub-analysis of PA levels by severity of haemophilia also revealed variable results. Two studies carried out in the last ten years found people with severe haemophilia to be more active than those with non-severe haemophilia (den Uijl et al., 2013, von Mackensen et al., 2016). Contrastingly, no differences in PA were found according to haemophilia severity across 10 studies (Heijnen et al., 2000, Köiter et al., 2009, Buxbaum et al., 2010, Groen et al., 2011b, Baumgardner et al., 2013, Niu et al., 2014, McGee et al., 2015, Bouskill et al., 2016, Goto et al., 2019, Timmer et al., 2020). This suggests that more severe haemophilia does not necessarily affect PA participation, which may reflect the positive influence of prophylaxis in reducing the risk of bleeds associated with PA. However, it is challenging to establish the true relationship between specific volumes of PA and the exact levels of prophylaxis that are required to reduce even a transient increase in the risk of bleeding. Information regarding the age at which prophylaxis was commenced, type, dosage and timing of prophylaxis, as well as adherence to treatment were inconsistent across studies. This limited the ability to draw conclusions regarding the influences of various aspects of treatment regimen on bleeds potentially related to PA. Broderick et al. (2012) proposed that considering

vigorous PA is usually only a small proportion of overall activity, the relative and overall risk of bleeding is low if the half-life of prophylaxis maintains factor levels above 50% for approximately 6-12 hours (Broderick et al., 2012). More robust reporting of details regarding treatment regimen in studies examining PA and bleeds is warranted, including the type of treatment product and potentially the factor half-life if available. It would be particularly interesting to compare PA and bleeding rates according to current treatments and novel therapies in future studies.

The AXIS and STROBE analyses revealed low to moderate quality and transparency of reporting on average, as well as various sources of bias amongst studies. Selection and non-response bias were common, but are difficult to control in observational research, especially in studies of rare genetic disorders such as haemophilia, where small sample sizes are a common limitation of research. Self-reported methods gave rise to potential measurement, social desirability and recall bias, which limits the interpretation of study findings. The use of objective measurement tools in future research has the potential to overcome such sources of bias. Potential confounding factors that may also influence PA participation include the severity of arthropathy, pain, a history of inhibitors and the presence of blood borne viruses. Such factors were described in some studies but not all, which warrants further consideration in future research.

Limitations of this review include a possible omission of studies due to the ambiguity of terminology used in the search strategy. However, reference lists of full texts and other reviews were additionally screened. Abstracts from conferences were not included due to the lack of complete data reported, although a proportion of these abstracts appeared to contain preliminary data from some of the final full texts included in this review. Interventional studies were not included considering they did not measure habitual PA, although this may have omitted studies which monitored the potential for adverse bleeding events in relation to exercise. Lastly, whilst all studies included in this review were observational, the majority were cross-sectional in nature, limiting the potential to determine causation between bleeds and PA. Only a small number of studies were prospectively designed, which highlights the need for more prospective longitudinal measurement of PA, bleeds and treatment regimen in future studies.

1.3.5 Conclusion

In conclusion, this systematic review suggests that levels of PA vary markedly between individual adults and children with haemophilia. However, it is clear that the quality of the evidence available to date has inherent limitation. There is significant heterogeneity between different studies with respect to study samples and methodology, as well as the common use of self-reported methods. In addition, due to the inherent inter-individual variability in bleeding tendency and treatment regimens amongst PwH, the relationship between bleeds and PA was difficult to elucidate. Longitudinal studies that encompass more rigorous assessment of PA and bleeds, comparing the impact of different treatment regimens and treatment products on these variables, represent an important clinical unmet need. This is particularly important given the increasing life expectancy of the haemophilia population and the rapidly evolving era of new therapies available.

1.4 Thesis aim

Based on the findings of the systematic review, the need for a more objective assessment of PA in adult PwH was identified. The relationship between bleeding phenotype and treatment regimen with PA was not clear based off the limited available evidence.

There is strong, established evidence of the benefits of PA for improving physical fitness and reducing chronic disease risk. The potential impact of bleeds and haemophilic arthropathy on physical functioning and PA in PwMSH may expose them to an increased risk of reduced physical fitness and chronic disease with age compared to the general population. This research proposal, in conjunction with the findings from the systematic review, inspired the aims and objectives of the research studies that were carried out for this PhD project.

The overarching aim of this project was to undertake a detailed examination of PA and physical health parameters in PwMSH, and to additionally investigate the relationship between PA and the clinical phenotype of adults with moderate and severe haemophilia. This was achieved through conducting a series of four studies which are outline in Figure 1.7. The methods used for each study are described in detail in Chapter 2. Individual studies are presented in Chapters 3-6. The clinical relevance of the collective study findings is contextualised and discussed in Chapter 7.

This PhD project was conducted as part of a larger scale study in Ireland called, “The Irish Personalised Approach to the Treatment of Haemophilia (iPATH).” The overall goal of the iPATH study was to make fundamental discoveries in relation to the biology of haemophilia, thereby enabling novel approaches to personalised treatment and management of haemophilia and haemophiliac arthropathy. Research conducted for this PhD was part of Work Package 1, which aimed to develop an integrated and comprehensive national registry for Irish patients with moderate and severe haemophilia, incorporating both deep clinical phenotype and whole genome sequence data. Overall, 105 PwMSH consented to the iPATH study for whole genome sequencing [i.e. 32% of the estimated national population of moderate and severe haemophilia, n= 330 (WFH, 2017)]. Of this, 54 PwMSH consented to participate in the iPATH Physical Activity Study (i.e. 26% of adults registered at the National Coagulation Centre, and 16% of the estimated national population of moderate and severe haemophilia of all ages). Ultimately, the iPATH Physical Activity Study contributed to the deep clinical phenotypic data generated as part of the integrated, comprehensive national registry of patients with moderate and severe haemophilia.

Figure 1.7: Outline of the studies in this thesis

Chapter 3: Study I: Physical activity and clinical phenotype in adults with moderate and severe haemophilia	•Primary aim: To determine physical activity participation in adults with moderate and severe haemophilia. •Secondary aim: To examine the relationship between physical activity and the clinical phenotype of moderate and severe haemophilia.
Chapter 4: Study II: Physical fitness and cardiometabolic risk in adults with moderate and severe haemophilia	•Primary aim: To determine physical fitness and cardiometabolic risk in adults with moderate and severe haemophilia. •Secondary aim: To examine physical fitness and cardiometabolic risk parameters in relation to physical activity and clinical phenotype.
Chapter 5: Study IIIa: An investigation of barriers to physical activity in adults with moderate and severe haemophilia	•Primary aim: To determine barriers to physical activity in adults with moderate and severe haemophilia. •Secondary aim: To examine barriers in relation to age, body composition, physical activity and clinical phenotype.
Chapter 5: Study IIIb: An investigation of pain and functional disability in adults with moderate and severe haemophilia	•Primary aim: To determine levels of pain and functional disability in adults with moderate and severe haemophilia. •Secondary aim: To examine the relationship between pain and functional disability with age, physical activity, body composition and clinical phenotype.
Chapter 6: Study IV: A follow-up of physical activity in adults with moderate and severe haemophilia during the Covid-19 pandemic	•Primary aim: To conduct a follow-up assessment of physical activity in adults with moderate and severe haemophilia from Study I. •Secondary aims: To determine if physical activity awareness had changed in participants since Study I, as well as the impact of the Covid-19 pandemic on physical activity levels.

Chapter 2: Methodology

2.1 Introduction

The World Health Organisation (WHO) proposes the International Classification of Functioning, Disability and Health (ICF) to provide a standard framework for the description of health and health-related states (WHO, 2002). This framework can be used to describe the different domains of health covered by the assessment battery of outcome measures used throughout the methods for this PhD project (see Figure 2.1). This chapter includes a detailed description of the methods used throughout this thesis. Some methods were common to individual studies (Table 2.1). Specific statistical methods used for each study are described in detail in each corresponding chapter.

2.2 Ethical approval

This research was conducted in accordance with guidelines of the World Medical Association (WMA) outlined by the Declaration of Helsinki (WMA, 2013). Ethical approval for all research conducted in this thesis was obtained from St. James's Hospital/ Tallaght University Hospital Joint Research Ethics Committee (Appendix IV). The General Data Protection Regulation (GDPR) 2018 came into effect in the European Union on the 25th of May 2018. The Data Protection Act 2018 [Section 36(2)] (Health Research) Regulations were updated to reflect this new legislation. Study documentation was subsequently amended according to institutional guidance on GDPR compliance (Appendix V). Recruitment and data collection for studies I-III were significantly disrupted by the Covid-19 pandemic from March 2020 onwards. Ethical approval was obtained to adapt the study in 2021 (Appendix VI).

2.3 Study design and sampling

All studies in this thesis involved an observational, cross-sectional study design. This allowed for the assessment of multiple outcomes at one time-point and prevented the requirement for participants to attend multiple research assessments. This was convenient, time-efficient and reduced the additional research burden on study participants. A convenience sampling approach to recruitment provided the best opportunity to maximise sample recruitment within the PhD timeframe, especially in light of the fact that haemophilia is a rare genetic disorder and the recruitment of large sample sizes may present challenges.

2.4 Study setting and timeframe

People with moderate and severe haemophilia (PwMSH) from the national haemophilia database at the National Coagulation Centre, St. James's Hospital Dublin, were invited to participate in the Haemophilia Study Group (HG). Healthy, male volunteers without haemophilia from the staff and student populations of St. James's Hospital, Tallaght University Hospital and Trinity College Dublin were invited to participate in the Control Study Group (CG). Recruitment and data collection for Studies I-III took place between March 2018-March 2020. Research assessments took place at the

Clinical Research Facility, St. James's Hospital. Recruitment and data collection for Study IV took place between June-December of 2021. This study was conducted remotely and did not require participants to attend in person for a face-to-face assessment.

Figure 2.1: The ICF framework application to haemophilia for this PhD project

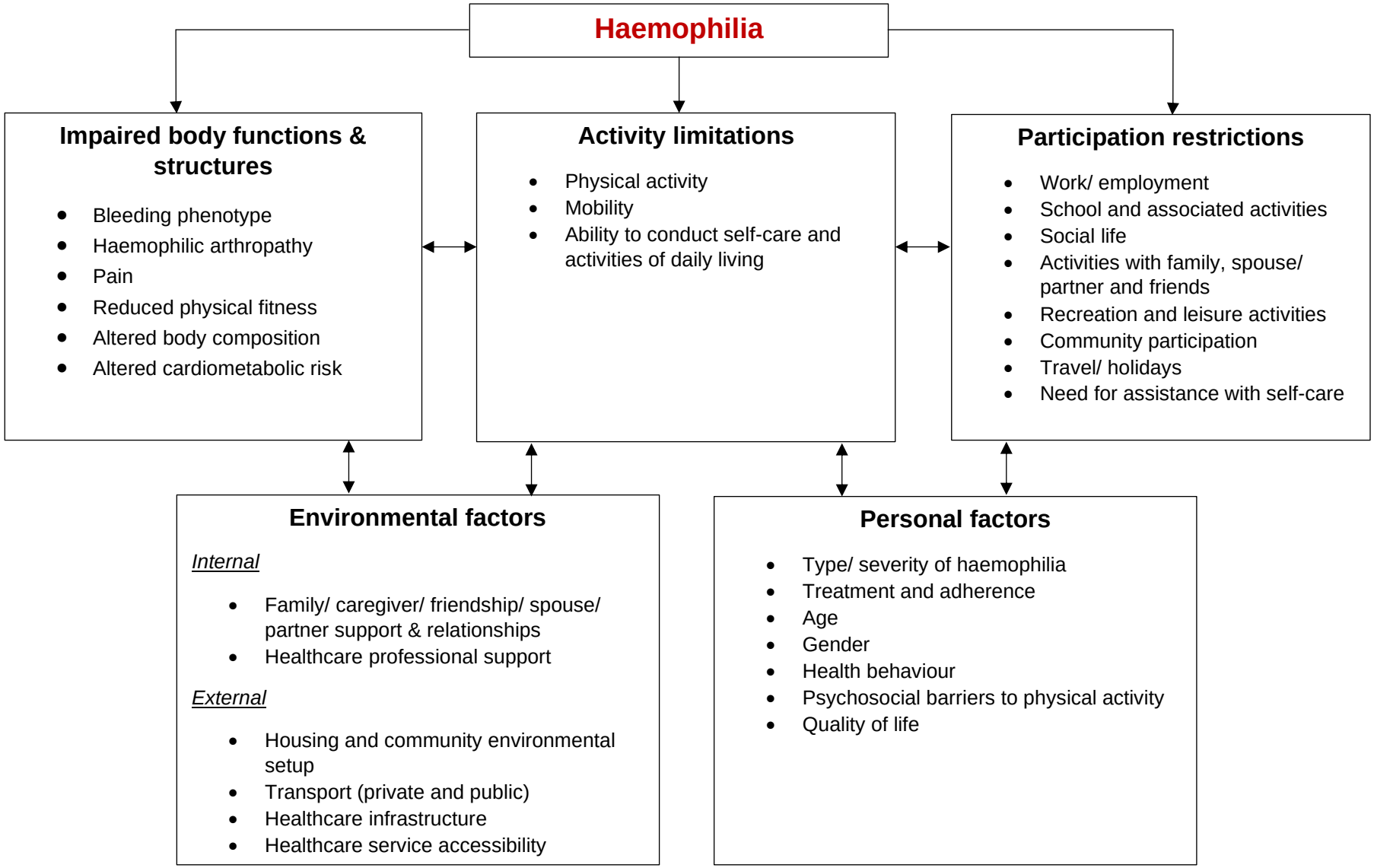


Table 2.1: Study procedures used in studies I-IV

Aim	Study I	Study II	Study III	Study IV
To determine:	Physical activity & clinical phenotype in PwMSH	Physical fitness & cardiometabolic risk in PwMSH	Barriers to physical activity in PwMSH	A follow-up of physical activity during the Covid-19 pandemic in PwMSH
Procedure				
Demographic information	✓	✓	✓	✓
Annualised Bleeding Rate	✓	✓	✓	
Haemophilia Joint Health Score	✓	✓	✓	
ActiGraph wGT3X-BT Accelerometer	✓	✓	✓	✓
Modifiable Activity Questionnaire	✓			✓
Anthropometry and body composition	✓	✓	✓	
Cardiometabolic disorder prevalence		✓		
Six-minute walk test		✓		
Grip strength		✓		
One leg stand test		✓		
YMCA cycle ergometer test		✓		
Blood pressure and arterial stiffness		✓		
Barriers to Being Active Quiz			✓	
The PROBE Questionnaire	✓	✓	✓	
Longitudinal follow-up questionnaire				✓

PROBE Patient Reported Outcomes Burdens and Experiences **PwMSH** People with moderate and severe haemophilia

2.5 Participant recruitment

Formal sample size calculations were not carried out a priori considering this was a cross-sectional study. Therefore, the aim was to maximise recruitment efforts during the project timeframe and achieve as large a sample as possible. People with haemophilia were screened for study eligibility by the clinical research team during routine outpatient appointments. Eligibility for study inclusion in the HG were as follows:

- A clinical diagnosis of moderate (1-5%) or severe (<1%) Factor VIII (Haemophilia A) or Factor IX (Haemophilia B) deficiency
- Male
- ≥18 years
- Capacity to provide informed consent
- Deemed safe to participate in clinical exercise testing using the Physical Activity Readiness Questionnaire (Appendix VII)
- No active inhibitors
- No acute or unresolved bleeds
- Ambulatory
- No acute musculoskeletal injuries
- No unstable cardiovascular/ respiratory/ metabolic disease
- No fitted electronic device (e.g. pacemaker)
- Deemed medically suitable by the clinical team

Healthy, male volunteers were invited to participate via an email and poster recruitment campaign. Eligibility for study inclusion in the CG were as follows:

- No diagnosis of haemophilia or any other inherited bleeding disorder
- Male
- ≥18 years
- Capacity to provide informed consent
- Deemed safe to participate in clinical exercise testing using the Physical Activity Readiness Questionnaire (Appendix VII)
- Ambulatory
- No history of neuro-musculoskeletal disease
- No history of HCV or HIV
- No acute musculoskeletal injuries
- No unstable cardiovascular/ respiratory/ metabolic disease
- No fitted electronic device (e.g. pacemaker)

All interested participants of both study groups were provided with the relevant Participant Information Leaflet (Appendix VIII). They were contacted one week later to determine study enrolment. Voluntary participation was emphasised. Participants were subsequently scheduled for a research assessment at a time and date most convenient for them. Study procedures, risks, benefits and data protection procedures were explained again to the participant as outlined in the information leaflet. Informed, written consent was obtained using the relevant Informed Consent Form (Appendix IX). A copy was also provided to the participant for their own records.

Patient and Public Involvement

The Irish Haemophilia Society is the national patient organisation for haemophilia and other inherited bleeding disorders in Ireland. Information regarding the study was presented at annual general meetings. Updates about the study were also communicated via the society newsletter.

2.6 Study procedures and outcome measures

2.6.1 Demographic information

The following demographic and clinical information was recorded, as appropriate:

- Age
- Type and severity of haemophilia (i.e. moderate or severe haemophilia A or haemophilia B)
- History of inhibitors
- Treatment regimen and the age at which prophylaxis was commenced
- HCV and HIV status
- Orthopaedic surgical history
- Bone health history (i.e. osteoporosis, osteopenia)

2.6.2 Clinical phenotypic parameters

A number of parameters involving the clinical phenotypic presentation of moderate and severe haemophilia were examined in this thesis. Reference to ‘clinical phenotypic parameters’ specifically throughout this thesis refers to the type and severity of haemophilia, bleeding phenotype, joint health and the age at which prophylactic treatment was commenced.

2.6.2.1 Bleeding phenotype: The Annualised Bleeding Rate

Significant heterogeneity in the definition and measurement of bleeding has been noted across the literature (Chai-Adisaksopha et al., 2015, Keipert et al., 2020). Furthermore, standardised diagnostic protocols or validated criteria to identify intra-articular joint bleeds are lacking (Timmer et al., 2015). Expert consensus groups report that bleeds are commonly diagnosed upon clinical presentation according to symptoms and location for the majority of cases, and also may be classified as major or minor bleeds (Blanchette et al., 2014, Fischer et al., 2017). Minor bleeds are usually self-diagnosed and treated as soon as possible at home. Major or life-threatening bleeds require

emergency medical treatment (Fischer et al., 2017). The classification of bleeds and other bleed-related terminology are summarised below in Table 2.2. based off standardised definitions from the literature (Donadel-Claeyssens, 2006, Blanchette et al., 2014, Fischer et al., 2014, Fischer et al., 2017).

Table 2.2: Definitions of bleeds in haemophilia

Term	Definition
Joint bleed	"An unusual sensation, 'aura', in the joint, in combination with any of the following: (a) increasing swelling or warmth of the skin over the joint; (b) increasing pain or (c) progressive loss of range of motion or difficulty in using the limb as compared with baseline."
Target joint	"Three or more spontaneous bleeds into a single joint within a consecutive 6-month period. Where there have been ≤ 2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint."
Muscle bleed	"An episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and loss of movement over baseline."
New bleed	"After an initial moderate to excellent response to treatment, a new bleed is defined as a bleed occurring > 72 hours after stopping treatment for the original bleed for which treatment was initiated."
Major bleed	"A major bleed is defined as a bleed characterized by pain, swelling, restriction of motion and failure to resolve within 24 hours of treatment.'"
Minor bleed	"A minor bleed is 'characterized by mild pain, minimal swelling, minimal restriction of motion, resolving within 24 hours of treatment.'"

Sources: Donadel-Claeyssens (2006), Blanchette et al. (2014), Fischer et al. (2014), Fischer et al. (2017).

Patients are generally advised to treat a bleed as soon as symptoms appear in order to reduce the potential for joint and soft tissue damage. Therefore, the majority of bleeds are not clinically diagnosed or verified in real-time as patients commonly treat themselves at home. Additionally, they may not always alert their haemophilia treatment centre when they experience a self-perceived bleed. PwMSH in Ireland are encouraged to use a smartphone application to scan clotting factor concentrate as it is used, whether it is intended for prophylactic treatment purposes or used to treat an acute bleed episodically. This application is linked to an electronic database at the haemophilia treatment centre, providing real-time information to clinical staff about when a patient uses treatment for a bleed. The clinical team contact the patient to obtain more information about bleeding events logged on the system. The success of this system is also heavily dependent upon patient adherence to scanning their treatment and reporting bleeding episodes. The self-reported recall of bleeds at clinical appointments may result in an under-reporting of bleeds. The accuracy of self-reported bleeds is also further dependent on how capable patients are in self-diagnosing and recognising distinctive signs and symptoms of a bleed compared to those of haemophilic arthropathy (Fischer et al., 2017). Mistaking pain or inflammation associated with haemophilic arthropathy as a bleed may potentially result in the over-treatment of non-bleeds and potentially an overestimation of bleed rate, although the signs and symptoms of both can be challenging for patients and their caregivers to distinguish. Common and distinguishing features of acute bleeds versus haemophilic arthropathy are

presented in Table 2.3, based off common definitions and features cited in the literature (Blanchette et al., 2014, Timmer et al., 2015, Hanley et al., 2017, Stephensen et al., 2018).

Table 2.3: Signs and symptoms of an acute bleed versus haemophilic arthropathy

Common	Acute bleed	Haemophilic arthropathy
Pain	• Early sign: Pain at end ROM • Moderate bleed: Increased intensity • Severe bleed: Severe intensity • Rapid resolution post-CFC infusion	• May be present during an acute flare-up or a chronic complaint • Improvement of pain is associated with activity soon after a period of rest
Swelling	• Moderate bleed: Some • Severe bleed: Marked	• May be present during an acute flare-up
Reduced joint range of movement	• Early sign: Minimal and difficult to distinguish from arthropathy • Moderate bleed: Some • Severe bleed: Almost complete restriction or a "joint immobilising bleed"	• May be present during an acute flare-up or a chronic complaint
Stiffness	• Presents as an early sign	• May be present during an acute flare-up or a chronic complaint
Warmth	• Presents as an early sign	• May be present during an acute flare-up
Fixed flexed position	Not applicable	• May be present during an acute flare-up or a chronic complaint
Additional signs and symptoms	• Redness • Muscle spasm • Early sign: Tingling sensation at end of joint range of movement • Prodromal sensation i.e. "aura" • Tense sensation • Early sign: Fullness • Inability to load the joint	• Locking • Bony enlargement • Impaired gait pattern • Muscular atrophy • Crepitus

Sources: Blanchette et al. (2014), Timmer et al. (2015), Hanley et al. (2017), Stephensen et al. (2018).

Bleeds were measured in Studies I-III using the Annualised Bleeding Rate (ABR), which is the recommended standard for the measurement of bleeding in haemophilia (Fischer et al., 2017). It is calculated as a count of bleeds over twelve consecutive months. The ABR is the most common measurement of bleeding across the literature, despite some variation in its calculation across studies (Chai-Adisaksopha et al., 2015). To calculate the individual ABR for each participant in this project, a retrospective audit of documented bleeding events from the electronic patient record was undertaken. Information was retrieved from the real-time smartphone application synced database

and electronic clinical records. To avoid under-reporting bleeds, all self-reported and clinically verified bleeding events were recorded. All retrospective bleeding events were recorded over the previous year in relation to each participants' respective research appointment. All types of bleed were included, including joint, muscle or visceral bleeds, although bleeding related to surgical or medical procedures were not counted. An Annualised Joint Bleeding Rate (AJBR) was also calculated based on joint bleeds alone. Bleeds were classified according to cause (i.e. spontaneous, traumatic or unknown) and verification status (i.e. clinically verified or not clinically verified). 'Traumatic bleeds' were defined as those with a definitive associated physical event that caused the bleed, which included physical impact, trauma or increased physical strain. 'Spontaneous bleeds' were defined as those with no apparent associated trauma. If the bleed did not fit the strict definition of a traumatic or a spontaneous bleed and no clear cause could be identified, the cause of the bleed was classified as 'Unknown'. Clinically verified bleeds were only defined as such if the participant was admitted to the treatment centre and if the bleed was clinically examined and formally diagnosed by the medical team. Bleeds that did not fit this criterion were classified as 'un-verified bleeds'. If a suspected bleed was ruled out according to ultrasound or clinical impression, the event was not counted as a bleed. Bleeds treated for a number of consecutive days in a row were classified as one bleed. A new bleed was a bleed occurring > 72 hours after stopping treatment for the original bleed for which treatment was initiated (Blanchette et al., 2014). Types of joints included in the AJBR were definitive joints cited as the wrist, elbow, shoulder, ankle, knee and hip. If a bleed was classified as a hand, finger, foot, upper or lower arm or leg bleed, this was not counted in the AJBR due to the ambiguity of this terminology.

2.6.2.2 Joint health: The Haemophilia Joint Health Score

Joint health encompasses the structural integrity and function of a joint (Gouw et al., 2019). It is routinely assessed and monitored in PwMSH using a variety of methods, including clinical examination, joint health scoring systems and radiographic joint imaging (Fouasson-Chailloux et al., 2018). Various methods of radiographic imaging, including Magnetic Resonance Imaging (MRI), X-Ray and ultrasound provide the most objective measurements of joint health status in PwMSH (Fischer et al., 2017). These methods were not feasible for use in this project due to their high cost and limited availability. A number of clinical joint health scores have been developed for estimating and monitoring the severity of haemophilic arthropathy. Such measures include the World Federation of Hemophilia Orthopaedic Joint Score, also known as the Gilbert Score (Gilbert, 1993, Fischer et al., 2017)], the Colorado Physical Examination Scale, the Petrini Joint Score and the Haemophilia Joint Health Score (HJHS). All capture similar domains of joint health.

Joint health in this thesis was measured using the HJHS. The HJHS was originally designed to measure and monitor mild joint disease in children and adolescents with haemophilia, however it is also the most extensively used non-radiographic joint health score in adults with haemophilia (Gouw et al., 2019). The currently used version (HJHS 2.1) scores individual elbow, knee and ankle joints in the following domains: Swelling (0-3); duration of swelling (0-1); muscular atrophy (0-2); crepitus

on motion (0-2); flexion loss (0-3); extension loss (0-3); joint pain (0-2); strength (0-4); and a global gait score (0-4) (Gouw et al., 2019). The maximum HJHS achievable is 124, with higher scores indicating more severe arthropathy, although specific cut-offs for joint disease severity have not been established (Sun et al., 2014, Gouw et al., 2019). The HJHS requires training, therefore the clinical specialist physiotherapists at the National Coagulation Centre measured the HJHS during routine outpatient clinics. The most recent HJHS for individual participants was recorded. The HJHS has demonstrated strong internal consistency, structural validity and reliability in children with haemophilia (Cronbach's alpha= .83-.84; Intra-class correlation coefficients >.70) (Hilliard et al., 2006, Fischer and de Kleijn, 2013, Teyssler et al., 2013, Groen et al., 2013a, Sun et al., 2014, Salim et al., 2016, Gouw et al., 2019, Feldman et al., 2011). The HJHS reportedly has moderate evidence for discriminant validity according to the age at which prophylaxis was commenced, the presence of synovitis and the continuous use of prophylaxis in adults with haemophilia (Khawaji et al., 2012, Kidder et al., 2015, Nijdam et al., 2016, Gouw et al., 2019). Conflicting evidence exists in mixed cohorts of adults and children for the correlation between the HJHS and radiographic joint imaging [HJHS and Magnetic Resonance Imaging: r= .27 (den Uijl et al., 2011); HJHS and Pettersson radiological (X-Ray) scores: r= .67 (Fischer et al., 2016); r= .86 (Fischer and de Kleijn, 2013)].

2.6.3 Physical activity

The measurement of PA is complex (Plasqui and Westerterp, 2007, Skender et al., 2016). Methods of PA assessment include behavioural observation, self-report (questionnaires, surveys, diaries/ logs), physiological measures (HR, body temperature, ventilation), and motion sensors (pedometers, accelerometers) (Westerterp, 1999, Schutz et al., 2001, Lamonte and Ainsworth, 2001, Plasqui and Westerterp, 2007, Skender et al., 2016). When selecting a measurement, it has been recommended that the PA parameter to be assessed (i.e. frequency, intensity, type or duration), the number of participants to be recruited as well as the burden, accessibility, cost and time efficiency of resources should all be considered (Strath et al., 2013).

Assessment methods of habitual PA in the free living setting include both subjective and objective measurement tools. A significant amount of variation has been reported on the level of agreement and association between subjective and objective methods of PA, ranging from weak to high (Prince et al., 2008, Kowalski et al., 2012, Skender et al., 2016). This reflects the diverse array of measurement tools available in both categories and the complexity of comparing one method versus another. Both categories of methods possess certain advantages and inherent limitations, however it has been recommended that objective and subjective measurements of PA used in combination have the potential to complement each other and provide a more complete representation of PA in the field setting (Skender et al., 2016).

2.6.3.1 Objective measurement of physical activity

The Doubly Labelled Water (DLW) method and Indirect Calorimetry (IC) have been recommended as criterion methods of PA energy expenditure measurement in the free-living and controlled

laboratory settings, respectively (Strath et al., 2013). During the DLW method, the participant ingests water containing specific quantities of two non-radioactive isotopes [oxygen-18 (^{18}O) and deuterium (^{2}H)] (Ainslie et al., 2003, Strath et al., 2013). The ^{2}H isotope is eliminated from the body as water, whereas the ^{18}O isotope is eliminated as both water and CO_2, therefore the rate of CO_2 production can be measured from the product of this difference over time (Ainslie et al., 2003, Strath et al., 2013). This, when combined with resting energy expenditure and the thermic effect of food, can be used to calculate PA energy expenditure (Strath et al., 2013). IC is measured via an open circuit system, where the participant breathes room air or a mixture of gases of known concentration. The amount of expired CO_2 and O_2 are measured and used to calculate energy expenditure and metabolism during rest or steady-state exercise (Ainslie et al., 2003, Strath et al., 2013). The use of criterion methods to measure PA was not feasible or practical for this project.

The ActiGraph wGT3X-BT (ActiGraph Corp, Pensacola, Florida, USA)

PA was objectively measured in this project using the ActiGraph wGT3X-BT, which is a lightweight (19g) and compact (4.6cm x 3.3cm x 1.5cm) triaxial accelerometer that measures PA acceleration across three axes [Vertical (V); Medio-lateral (ML); Anterior-posterior (AP)] (Figure 2.1). Activity counts collected across all three planes of acceleration are converted into a composite digital unit called 'vector magnitude' [VM3= $\sqrt{(V^2 + ML^2 + AP^2)}$]. VM3 indicates the intensity of PA undertaken (Sasaki et al., 2011, Kelly et al., 2013). The device contains a three-axis micro-electromechanical system accelerometer that samples acceleration data by a 12-bit analogue to digital converter at rates ranging from 30Hz to 100Hz (ActiGraph, 2020). Data is stored in a raw, non-filtered accumulated format and raw data is processed using its companion software [ActiLife 6 (ActiGraph Corp, Pensacola, Florida, USA)] to determine VM3 counts at the user-desired epoch length (ActiGraph, 2020). The device uses the VM3 and programmed algorithms to detect an individual's position (i.e. standing, lying, or sitting) and to ascertain whether they are wearing the device or not (John and Freedson, 2012). The ActiGraph has been validated in the laboratory setting in healthy adults and has been shown to be strongly correlated with oxygen consumption measured via IC ($r = 0.810$, $p < .001$) (Kelly et al., 2013). Moderate to strong correlations between various parameters of ActiGraph measured energy expenditure and DLW measured energy expenditure have also been demonstrated in the free living setting (Chomistek et al., 2017). The ActiGraph has also been deemed reliable for the assessment of PA in the free-living setting (Aadland and Ylvisåker, 2015).

ActiGraph wGT3X-BT protocol

The ActiLife software (Version 6.13.4) was used to initialise the devices. Participant details, coded by their study ID number, were programmed to the monitor including date of birth, gender, ethnicity, height, weight, wear position and the date PA monitoring was due to commence. Acceleration was selected to be sampled at a frequency of 30 Hz. The device was worn attached to an elasticated belt over the right anterior superior iliac spine with the micro USB port facing upwards (Trost et al., 2005). Participants were instructed to wear the monitor for seven consecutive days during waking hours only, which is the most common protocol used in previous research (Skender et al., 2016).

Participants were advised to remove the monitor while sleeping, when showering and during any other water-based activities. It has been previously suggested that wearing an accelerometer may increase PA, as participants are aware that they are being monitored (Skender et al., 2016). Therefore, it was emphasised to participants to try to maintain their typical levels of PA during the week. Participants were provided with an information leaflet detailing the procedures for wearing the monitor (Appendix X). A PA diary was also provided to record daily non-wear time and any PA performed during non-wear time (e.g. sleeping, swimming, showering) (Appendix XI). This diary was used to validate wear-time from the accelerometer raw data with wear-time reported by the participant. Lastly, participants were provided with a pre-stamped and addressed envelope to facilitate return of the monitor and PA diary when completed.

Figure 2.2: The ActiGraph wGT3X-BT accelerometer

ActiGraph wGT3X-BT data analysis

The ActiLife software (Version 6.13.4) was used to download and process raw data from the monitors. Raw data was analysed in 60 second epochs. Wear-time validation algorithms by Choi et al. (2011) were applied to the data to identify and filter out periods of non-wear. Non-wear time is estimated by analysing periods of little or no PA according to an algorithm (i.e. minimum length 90 minutes, small window length 30 minutes, spike tolerance 2 minutes), in order to determine whether the participant was actually wearing the device or not (Choi et al., 2011). Device compliance can affect the accuracy and comparability of results using accelerometers, therefore wear-time inclusion criteria of ≥ 10 hours per day on ≥ 4 days (including one weekend day) was applied to raw data for analysis. This wear-time criteria has been commonly applied in many previous studies and is recommended for data analysis in adults (Skender et al., 2016, Migueles et al., 2017). Conflicts between the device's inbuilt wear-time sensor and the Choi et al. (2011) algorithm were manually reviewed and compared using the PA diary. The following cut-points established by Troiano et al. (2008) for adults were applied to determine PA intensity: Sedentary activity= 0-99 counts per minute (cpm); Light PA= 100 – 2019 cpm; Moderate PA= 2020 – 5998 cpm; Vigorous PA= ≥5999 cpm. Bouts of combined moderate-vigorous PA sustained for at least 10-minutes at a time (i.e. Freedson bouts) were analysed according to a minimum cut-point of 1952 cpm, with drop-time of two minutes below this threshold permitted per bout (representing a brief interruption to activity) (Freedson et al.,

1998). Moderate-vigorous PA output was classified according to the achievement of PA guidelines via the total duration of moderate-vigorous PA per week (Bull et al., 2020), and via the duration of moderate-vigorous PA achieved per week in Freedson bouts.

Despite the numerous advantages of objectively measuring PA, accelerometers are not without limitations. There is a general scarcity of validation studies across the literature for the use of accelerometers in chronic disease and orthopaedic populations (Van Remoortel et al., 2012, Yu et al., 2015). Two previous studies have attempted to validate accelerometers in children with haemophilia amongst a mixed sample of children with chronic diseases (Takken et al., 2010, Walker et al., 2015). Three studies have used various accelerometers to assess habitual PA in children with haemophilia (Buxbaum et al., 2010, González et al., 2011, Bouskill et al., 2016) and two recent studies have used accelerometry in adults with haemophilia (Putz et al., 2021, Timmer et al., 2020). Putz et al. (2021) identified a moderate, inverse correlation between the HJHS and vigorous PA measured by the ActiGraph in adult PwMSH (r_s= −.56, p = .048). Lastly, accelerometers are limited in their ability to measure certain types of PA like swimming, cycling or resistance training (Kowalski et al., 2012, Skender et al., 2016) and therefore may underestimate these types of PA.

2.6.3.2 Subjective measurement of physical activity

Self-reported questionnaires offer a convenient, low cost, time-efficient means of assessing various domains and dimensions of PA, and are generally used for large scale studies. Self-reported questionnaires are recommended as a useful adjunct to objective measures in order to provide a more complete picture of PA; however, they are susceptible to recall bias, social desirability bias and possess low levels of validity for the assessment of PA in the free-living setting (Strath et al., 2013). It has also been reported that questionnaires may over or under-estimate PA depending on the complexity of subjective data collected (Skender et al., 2016). As mentioned, objective measurement tools such as accelerometers are limited by a lack of contextual information in identifying specific types of PA being undertaken. This was particularly important to consider for this project, as people with haemophilia are generally recommended to partake in activities that involve low risk of physical impact (such as swimming and cycling) in order to reduce the risk of bleeds and prevent joint damage (Srivastava et al., 2020). Bearing in mind the ActiGraph accelerometer provided detail on the frequency, intensity and duration of PA, more information about the types of PA undertaken by study participants was required. A large number of PA questionnaires exist, however the questionnaire best suited to obtain information about types of PA for this project was the Modifiable Activity Questionnaire (MAQ).

The Modifiable Activity Questionnaire

The MAQ is a retrospective questionnaire which measures the frequency, duration and types of PA undertaken by an individual over the previous year. This tool was deemed most appropriate for this project as it can be easily adapted and modified to be suitable for a variety of populations (Kriska et al., 1990, Pereira et al., 1997) (Appendix XII). Participants were asked to select specific activities or sports they have taken part in regularly in the previous year from a pre-specified list of activities.

Participants were asked to record the number of months per year, the number of times per month and the duration of time spent in each activity. Additional questions were added regarding childhood participation in PA and sport. The version of this questionnaire provided to PwMSH also asked participants whether they took additional prophylaxis prior to participation in PA or sport. Moderate to strong reliability and reproducibility have been demonstrated for the MAQ in adults (r= 0.62-0.97) (Kriska et al., 1990, Delshad et al., 2015). Validity of the MAQ has also been established, demonstrating moderate to strong correlations with DLW (0.52-0.74) (Schulz et al., 1994), activity monitors (0.62) (Kriska et al., 1990) and other subjective measurements of PA (0.49) (Kriska et al., 1990).

2.6.4 Physical fitness

The American College of Sports Medicine (ACSM) defines physical fitness as the ability to carry out daily activities with sufficient energy, vigour and alertness, without significant fatigue (Committee, 2008, Riebe et al., 2018). Physical fitness involves numerous components including cardiorespiratory power and endurance, muscular strength and endurance, balance and flexibility (Riebe et al., 2018).

2.6.4.1 Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) depends on the physiological and functional ability of the cardiovascular and respiratory systems to deliver O_2 to large, exercising muscle groups over a sustained period of time (Riebe et al., 2018). The standard criterion measure of CRF is the maximal volume of oxygen consumed per unit of time (VO_{2max}), which may be expressed in relative ($mL \cdot kg^{-1} \cdot min^{-1}$) or in absolute ($mL \cdot min^{-1}$) terms. VO_{2max} is measured using IC during a graded, incremental, maximal exercise test to volitional exhaustion (Riebe et al., 2018). An individual's VO_{2max} indicates their true physiological limit (McArdle, 2015, Riebe et al., 2018). A wide variety of maximal and submaximal laboratory and field-based exercise tests exist which can be used to indirectly estimate VO_{2max} or provide some indication of an individual's CRF (Riebe et al., 2018). Submaximal exercise testing aims to determine heart rate (HR) response to one or more submaximal work rates and uses the results to predict VO_{2max} (Riebe et al., 2018). This is based off the assumptions that a steady state HR is obtained at each stage of exercise work rate and a linear relationship exists between HR and work rate (Riebe et al., 2018).

Lower limb arthropathy may limit the ability to establish maximal CRF in adults with haemophilia due to pain, restricted joint range of movement, peripheral muscular weakness or atrophy, and fear of injury or bleeding. Maximal exercise testing, mostly using cycle ergometer protocols, has been used to measure CRF successfully in children and adolescents with haemophilia, with minimal or no adverse events (Koch et al., 1984, Falk et al., 2000, van der Net et al., 2006, Engelbert et al., 2008, Douma-van Riet et al., 2009, Groen et al., 2011a, Li et al., 2016, Sondermann et al., 2017). Limited information exists across the literature on the safety and feasibility of maximal CRF testing in adult PwMSH. The majority of a small group of adults with severe haemophilia discontinued a maximal treadmill test due to pain, peripheral muscle fatigue, fear of bleeds and an adverse nosebleed event

in a study by Herbsleb and Hilberg (2009). The uncertainty regarding the safety and feasibility of maximal exercise testing in adults with haemophilia was further resounded by Vallejo and colleagues, who reported that participants were not able to complete a treadmill or cycle ergometer fitness test piloted by their study group. This ultimately led to the decision to use a field walking test, which was better tolerated (Vallejo et al., 2010). Contrastingly, no adverse events were found in a study by Groen et al. (2013b), who used a maximal cycle ergometer test in 15 young adults with haemophilia, however participants had mild and moderate haemophilia, thus were likely less burdened by bleeds and haemophilic arthropathy. A lack of consensus on the safety of maximal exercise testing in adults with moderate or severe haemophilia informed the decision to use submaximal exercise testing methods to assess fitness in this project. As previously mentioned, low impact types of exercise and PA, such as walking and cycling, are generally recommended for people with haemophilia. Therefore, submaximal exercise field tests involving walking and cycling were chosen to best reflect CRF and functional aerobic capacity in PwMSH in this project.

The Six-Minute Walk Test

Field walking tests have been used to measure functional capacity in people with haemophilia in previous studies, including the Two-Minute Walk Test (Lobet et al., 2019), the 12-Minute Walk Test (Czepa et al., 2012, Czepa et al., 2013, Runkel et al., 2016) and the Multistage Fitness Test (20m Shuttle Walk) (Broderick et al., 2010). The Six-Minute Walk Test (6MWT) is the most commonly used test across both paediatric (Douma-van Riet et al., 2009, Hassan et al., 2010, Radzevič et al., 2013, Eid et al., 2014, Eid and Aly, 2015, Stephensen et al., 2016, Castaño et al., 2017, El-Shamy and Abdelaal, 2018, Hashem et al., 2019) and adult populations with haemophilia (Salim et al., 2016, Castaño et al., 2017).

The 6MWT was originally developed for patients with respiratory disease, although it has been used in other arthritis and orthopaedic populations. It has been shown to be a good predictor of function after total knee replacement (Ko et al., 2013), as well as reliable and responsive to change in the osteoarthritis population (Kennedy et al., 2005, French et al., 2011). Although the 6MWT has not been formally validated in PwMSH, it was considered that this test would likely be tolerated well amongst differing degrees of haemophilic arthropathy. The 6MWT takes a relatively short amount of time to administer and the pace of exertion is self-selected. The 6MWT therefore offered a safe, simple and time efficient measure that would provide an indication of CRF in study participants. Furthermore, the 6MWT provided a more functional representation of aerobic capacity, which may be more relevant in the clinical context. Testing procedures were conducted in accordance with the American Thoracic Society (ATS) guidelines (ATS, 2002).

Six-Minute Walk Test protocol

Equipment:

- A 30m pre-measured flat walking area with interval markings every three metres
- Cones to mark boundaries of the course
- Pulse oximeter for measuring HR and oxygen saturation (SpO_2)

- The Borg Scale to measure the rate of perceived exertion (RPE; Appendix XIII)
- Stopwatch
- Clicker for measuring laps of 30m
- Tape measure

Procedure:

1. The testing procedure was explained to the participant and they were given the opportunity to ask questions. During the test the participant was asked to walk continuously for six minutes along a 30m pre-measured walkway at a self-selected pace. They were advised to cover as much distance in six minutes as possible. They were advised they could stop the test at any time, especially if pain, excessive dyspnoea, dizziness or any other symptom of malaise arose.
2. Resting HR, SpO_2 and RPE were assessed before, during and after the test at standardised intervals.
3. During the test, laps of 30m were counted using a clicker, and encouragement was provided at standardised intervals.
4. Upon test completion at six minutes, the participant was asked to stop wherever they were, and the researcher marked and measured the final distance covered.
5. Vitals and the rate of perceived exertion were measured immediately upon test completion. This was repeated after the participant was allowed to rest for five minutes.

The YMCA cycle ergometer test

Cycle ergometers provide a non–weight-bearing exercise testing modality that allows work rates to be adjusted in small increments, meaning load and intensity of the testing protocol can be gradually adjusted for the individual (Riebe et al., 2018). The YMCA cycle ergometer protocol uses two to four three-minute stages of continuous exercise with a constant pedal rate of 50 rotations per minute (rpm) (Riebe et al., 2018). The protocol and work rate adjustment is based on the participant's steady state HR [<5-6 beats per minute (bpm)] at the end of Stage 1 (Figure 2.2). When two consecutive work stages of a HR between 110 and 85% of the individual's HR_{max} have been achieved, the test is complete. The participant's VO_{2max} can then be estimated using an extrapolation equation. Predicted VO_{2max} measured by the YMCA cycle ergometer test has been shown to correlate moderately with maximally determined VO_{2max} [r= .77; (Beekley et al., 2004), r= .65 (Jamnick et al., 2016); r= .68 (Garatachea et al., 2007)]. The YMCA test was chosen because the magnitude of increase in resistance at each stage was lower than other commonly used submaximal testing protocols (e.g. the Astrand-Rhyming Cycle Ergometer Test). It was therefore deemed that the difficulty of the test would increase more gradually, making it more comfortable and less inclined to fatigue participants too quickly. This fitness test was intended to be conducted as part of a separate pilot study for this thesis. Data collection had commenced for the control group, however recruitment and data collection in PwMSH was disrupted by the Covid-19 pandemic. Therefore, regression was used to

predict VO_{2max} in participants with haemophilia using an equation based off normative 6MWT and VO_{2max} results (further detail provided in Chapter 4).

YMCA cycle ergometer test protocol

Equipment:

- Electronically braked cycle ergometer (COSMED Ergoline, GMbH, Germany; Figure 2.3)
- Blood pressure monitor (Connex® Vital Signs Monitor, Welch Allyn Inc. Skaneateles Falls, New York, USA)
- Polar HR monitor (Figure 2.4)
- The Borg Scale to measure the RPE (Appendix XIII)

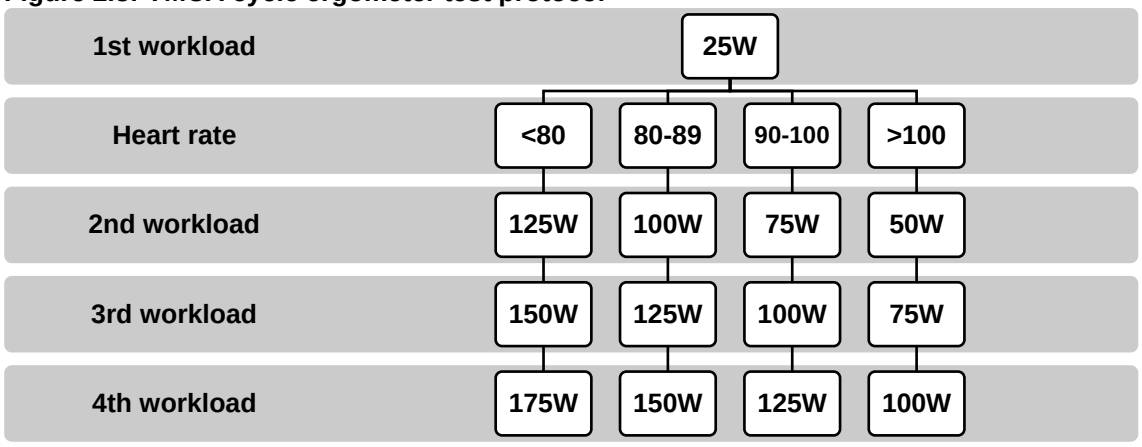
Procedure:

1. The test was first explained to the participant and they were given an opportunity to ask questions. They were informed that they could stop the test at any stage, and to alert the researcher if they experienced any excessive shortness of breath, pain or discomfort in the chest/ head/ jaw or shoulder, generalised pain, dizziness, nausea or malaise.
2. The seat height was adjusted to the participant's leg length so that the knee was slightly bent with the ball of the foot on the pedal when the pedal was at its lowest point.
3. The participant was allowed to practice the pace of 50 rpm during a three-minute warm up at 0 Watts (W).
4. The initial workload was set to 25W during the first stage of the test.
5. The participant began to cycle until a steady-state HR was achieved (i.e. a difference of no more than 5-6 bpm).
6. HR was measured during the last 15-30 seconds of the 2nd and 3rd minute. If HRs differed by more than 5 bpm an extra minute was added to the stage until steady-state HR was achieved. Once this was achieved, the workload was adjusted at each stage of the test according to the protocol (Figure 2.2).
7. HR, BP and RPE were monitored and recorded at the end of each stage.
8. Steps 6 and 7 were repeated until two consecutive stages of steady-state HR between 110 and 85% HR_{max} were achieved. When this was achieved, the test was complete and the workload was gradually reduced during a cool down until the participant's HR returned to near resting values. HR, BP and RPE were monitored and recorded for 5-10 minutes after the test.

Scoring:

Microsoft excel was used to plot the averages of the steady-state HRs in the last two consecutive stages of the test (y-axis) against the workload (x-axis). A vertical line was drawn at the estimated HR_{max} (208-0.7 x age) to bisect the diagonal line joining both HRs to estimate maximal workload. Estimated maximal work load, along with body weight, was then input into the ACSM leg ergometer equation [(10.8* (max workload)/ body weight) +7] to estimate $VO_{2max.}$ (Riebe et al., 2018).

Figure 2.3: YMCA cycle ergometer test protocol



W Watts

Figure 2.4: COSMED ergoline cycle ergometer

Figure 2.5: Polar heart rate monitor

2.6.4.2 Strength

Muscular strength is defined as the ability of muscle to exert force (Riebe et al., 2018). The criterion standard measure of strength is known to be the One-Repetition Maximum (1-RM), which is a dynamic assessment of the greatest resistance that can be moved through the full ROM in a controlled manner with good posture (Riebe et al., 2018). The safety and feasibility of this type of strength testing has not been ascertained in people with haemophilia.

Grip strength

Static or isometric maximum voluntary contraction is the most commonly used method to assess muscular strength across various populations with haemophilia (Hilberg et al., 2001, González et al., 2007, Engelbert et al., 2008, Douma-van Riet et al., 2009, Runkel et al., 2016, Stephensen et al., 2016, Sondermann et al., 2017, Hashem et al., 2019, Lobet et al., 2019, Calatayud et al., 2020, Goto et al., 2015, Al-Sharif et al., 2014). Grip strength measured using handheld dynamometry was the most convenient and time efficient method available to provide a measurement of the general strength of participants in this project. Although isometric grip strength is specific to muscles of the hand and upper limb, reduced grip strength has been recognised as a predictor of mortality and poorer health outcomes in the general population (Celis-Morales et al., 2018). It also provides an indication of overall muscle strength [correlations with elbow flexion strength (r = .67), knee extension strength (r = .51), and trunk extension strength (r= .54)] (Rantanen et al., 2003). Previous studies have recommended the Jamar hand-grip dynamometer as a valid and reliable measure of grip strength in healthy individuals (Mathiowetz et al., 1984, Lusardi and Bohannon, 1991, Beaton et al., 1995, Roberts et al., 2011). It also has excellent intra and inter-rater reliability (ICC 0.85-0.98) (Peolsson et al., 2001, Bohannon and Schaubert, 2005, Sousa-Santos and Amaral, 2017).

Jamar hand-grip dynamometer protocol

Equipment:

- Chair (no arm rests)
- Jamar Smart Hand Dynamometer (Figure 2.5)

Procedure:

1. The participant was asked to remove any hand or wrist jewellery.
2. They were seated in the chair and instructed to sit upright with their head level, back against the chair and feet flat on the ground. The shoulders were adducted and neutrally rotated, the elbows were flexed at 90° and the forearms and wrists were held in neutral (ASHT, 1992, Heyward and Gibson, 2014).
3. The grip handle was adjusted appropriately for the participant so that the distal and proximal interphalangeal joints of the index finger were at approximately 90°.
4. The testing procedure was explained to the participant and a gentle, submaximal practice trial was allowed to ensure they fully understood the procedure and to check functionality of the dynamometer. It was emphasised that the participant should not hold their breath during maximal exertions (to avoid the Valsalva manoeuvre). They were also told that they could stop the test at any point if the test caused any pain.
5. During the test, the participant was asked to squeeze the hand-grip dynamometer as tightly as possible until the numbers on the monitor ceased to increase.
6. Standardised encouragement was given to the participant by the researcher.
7. Three trials on both dominant and non-dominant sides were assessed with a 30-second rest between tests on each side.

Scoring:

The best of three trials was taken as the final score. Results were also categorised according to whether there was a >10% discrepancy between the dominant and non-dominant sides (Petersen et al., 1989).

Figure 2.6: Jamar smart hand dynamometer

2.6.4.3 Balance

Balance is defined as the maintenance of equilibrium during a stationary or moving state (Riebe et al., 2018). Balance may be altered in adults with haemophilia who have significant lower limb arthropathy. A simple balance test was selected to measure advanced, static balance uniformly across both study groups.

The One Leg Stand Test

The One Leg Stand Test (OLST) is the most commonly used measure of balance in previous studies of adults and children with haemophilia (Hilberg et al., 2001, Czepa et al., 2012, Czepa et al., 2013, Runkel et al., 2016, Stephensen et al., 2016). The OLST has been validated by its relationship with frailty, gait, falls risk and activities of daily living (Bohannon, 2006, Heyward and Gibson, 2014). Satisfactory within and between test repeatability in people with haemophilia has been reported (ICC: 0.78-0.85) (Stephensen et al., 2016). The OLST, however, has not been formally standardised and variation has been found to exist between testing procedures and cut-off times for various age groups (Bohannon, 2006). A cut-off time of 30-seconds has been used in a previous study assessing balance in adults with haemophilia, and was therefore applied (Czepa et al., 2012).

One Leg Stand Test protocol

Equipment:

- Stopwatch
- Fixed surface (i.e. a chair or table) for support

Procedure:

1. The participant was instructed to stand beside a fixed counter-top.
2. With their shoes on and eyes open, the participant was instructed to hold onto the side of the counter and lift their non-testing leg off the floor whilst maintaining their hip and knee at a 90° angle.
3. This procedure was explained to them and they were allowed one practice trial.
4. The researcher stood in close proximity to the participant for safety. Participants were instructed to lift the supporting hand from the counter and maintain their balance for as long as possible.
5. The stopwatch was started from the moment the participant's hand was lifted. The test ended if they reached the 30 second cut-off point or if their non-testing foot came in contact with the floor. The test was repeated on both legs. Successful or unsuccessful completion of the test was recorded.

2.6.5 Additional cardiometabolic risk factors

Hypertension, hyperlipidaemia, insulin resistance and being overweight or obese are amongst the leading established risk factors for cardiometabolic diseases (Murray et al., 2020). These additional

risk factors were profiled in the present study to ascertain further detail on cardiometabolic risk in study participants. Body composition and blood pressure were measured. Cardiometabolic risk disorder prevalence (hypertension, insulin resistance) was also recorded. As many participants were travelling long distances to the hospital on the day of their scheduled research assessment, blood sampling of fasting glucose and lipids was not logistically feasible.

2.6.5.1 Body composition

Body Composition (BC) describes the relative amounts of muscle, fat, bone and other vital components of body structure (Riebe et al., 2018). Criterion methods for BC assessment include Densitometry (via Hydrostatic Weighing and Air Displacement Plethysmography), Computed X-ray Tomography (CT), MRI and Dual-Energy X-Ray Absorptiometry (DXA) (Duren et al., 2008, Heyward and Gibson, 2014, Klein et al., 2007). The use of these methods was not feasible for the present study due to the high cost of specialised equipment and expertise required to conduct these assessments. BC was therefore measured using anthropometry and bioimpedance analysis (BIA). These methods are more convenient, time-efficient, relatively inexpensive and more clinically accessible, which could facilitate longitudinal monitoring of BC in the haemophilia population.

Anthropometry

Anthropometry is the simplest means of BC assessment that involves the measurement of body mass, size and shape, providing an estimate of overall adiposity in an individual (Duren et al., 2008). Body weight is the most basic general measure of obesity, assuming that increased weight infers increased fat mass (FM), however changes in body weight may be due to body water, FM or lean tissue mass (LTM) (Duren et al., 2008). Overcoming the limitations of weight alone, body mass index (BMI; kg/m^2) categorises individuals by weight relative to their height. The World Health Organisation (WHO) classifies BMI in adults (>20 years old) according to the following categories: Underweight (<18.5); normal (18.5-24.9); pre-obesity/ overweight (25.0-29.9); obesity class I (30.0-34.9); obesity class II (35.0-39.9); and obesity class III (>40) (WHO, 2021). BMI offers a simple and relatively standardised measure of BC comparable with other research, although the correlation between BMI and gold standard measures has been known to vary depending on different modalities and sites of measured adipose tissue mass [MRI and BMI, r= 0.313-0.888 (Chan et al., 2003); CT and BMI, r= 0.81-0.89 (Boos et al., 2015)]. Furthermore, BMI cannot differentiate between FM and LTM, therefore individuals with high LTM (e.g. athletes) may be categorised as obese, whilst those with low LTM and high FM (e.g. patients with cancer), may be misclassified as having a normal BMI (Duren et al., 2008, Heyward and Gibson, 2014). Considering this limitation, the use of additional anthropometric indices involving waist circumference (WC) were measured for this project, including WC itself, hip circumference (HC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR). These measurements were chosen in order to provide more information about FM distribution, particularly central abdominal adiposity, which is a sensitive predictor of cardiometabolic risk (Klein et al., 2007, WHO, 2011, Riebe et al., 2018, Després, 2012, Heyward and Gibson, 2014, Jayedi et al., 2020). Moderate to strong correlations have been demonstrated between various measurements of BC [BMI

and WC: r= .86-.94 (Ford et al., 2003); MRI and WC, r= .44-.86 and MRI and WHR: r= .43-.72 (Chan et al., 2003); and WHtR and DXA: r= .79 (Staynor et al., 2020)].

Anthropometry protocol

Procedures for the measurement of height and weight were adapted according to guidelines recommended by the ACSM (Riebe et al., 2018).

Height

Height was measured barefoot using a stadiometer (SECA 763 stadiometer, SECA, Hamburg, Germany), according to the following procedure:

1. The participant was instructed to remove their shoes and socks. They were advised to stand with their feet together on the footplate of the stadiometer, with the arms by their sides and their gaze directed straight ahead, looking forward in the horizontal plane.
2. Height was measured upon a maximum inhalation.
3. Height was recorded from a single measurement in centimetres (cm) to the nearest millimetre (mm).

Weight and BMI

Weight and BMI were measured using the SECA mBCA 515 Multi-Frequency Body Composition Analyzer (Seca, Hamburg, Germany) (Figure 2.6).

1. The participant was asked to ensure their pockets were empty and to remove any heavy clothing or jewelry before stepping on to the device.
2. The device was pre-programmed to account for clothing by subtracting 0.5kg from weight measured.
3. Weight was measured and recorded in kg.
4. This device also calculated the participant's BMI (kg/m^2) when height was inputted. BMI was classified according to WHO classification (WHO, 2021).

Anthropometric indices involving waist circumference

WC and HC were measured using a flexible, inelastic tape according to guidelines recommended by the WHO (WHO, 2011). Measurements were recorded in cm.

1. The participant was asked to stand with their feet together, arms by their side with the body weight evenly distributed.
2. HC was measured around the widest portion of the buttocks, with the tape parallel to the floor. A mirror was used to check that the tape was parallel to the floor on the blind-side of the researcher.

3. WC was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest at the end of a normal exhalation. Again, a mirror was used to check that the tape was parallel to the floor on the blind side of the researcher.
4. Each measurement was repeated twice and the average of the two measurements was calculated. If measurements differed by more than 1cm, the measurement was repeated a third time.
5. WHR and WHtR were calculated using anthropometric variables as appropriate (WHR= WC/HC; WHtR= WC/height).
6. All anthropometric values were compared with recommended cut-offs for men, as applicable (Table 2.4) (WHO, 2011, Jayedi et al., 2020).

Table 2.4: Cut-off points for waist circumference anthropometric variables

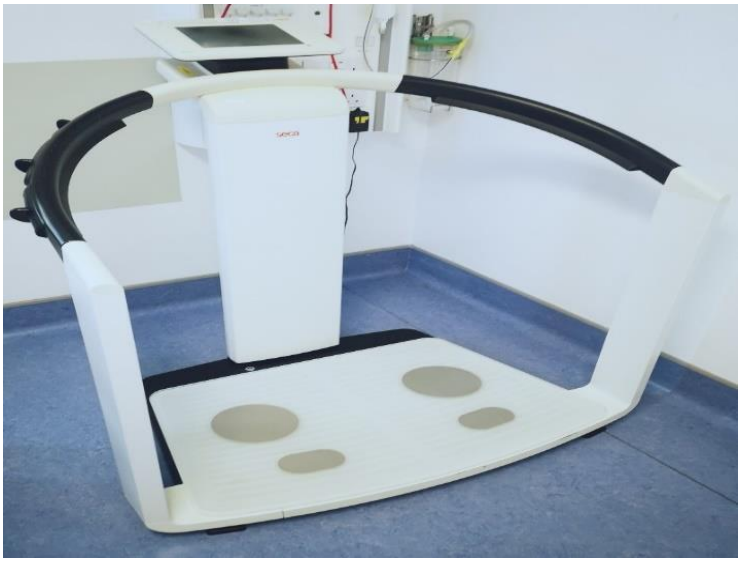
Indicator	Cut-off points	Risk of metabolic complications
Waist circumference (cm)	>94	Increased
Waist circumference (cm)	>102	Substantially increased
Waist-to-hip ratio	>.90	Substantially increased
Waist-to-height ratio	<.50	Increased

Sources: WHO (2011), Jayedi et al. (2020).

Bioimpedance analysis

BIA is a time-efficient, non-invasive, and relatively inexpensive method of BC assessment (Heyward and Gibson, 2014). It is based on the principle that electric current flows more easily through water compared with other tissues, such as fat, which provide more resistance to electric current (Dehghan and Merchant, 2008). The majority of the body is composed of water ions, thus low level electric current passes through various tissues of the body at different rates. Depending on water content and tissue composition, an estimate of BC is calculated using predictive equations [i.e. FM, LTM, skeletal muscle mass (SMM) etc.] (Wagner and Heyward, 1999, Dehghan and Merchant, 2008, Heyward and Gibson, 2014). BIA has been shown to correlate highly (>0.95) with reference methods for fat free mass when conducted in controlled conditions, although limits of agreement have been found to vary (± 5-10%) (Wan et al., 2014). A number of factors may impact BIA results, including recent food or water intake, hydration status, recent strenuous exercise, and hand and foot contact with electrodes (Dehghan and Merchant, 2008). Therefore, participants were asked to refrain from eating any heavy meals directly before the assessment, to refrain from drinking caffeinated beverages within 12 hours of the assessment, to refrain from drinking alcoholic beverages or undertaking strenuous PA within 24 hours of the assessment, and lastly to void completely prior to the assessment. A validated BIA device, the SECA mBCA 515 Multi-Frequency Body Composition Analyzer (Seca, Hamburg, Germany) was available for use in the present study (Figure 2.6) (Peine, 2013, Bosy-Westphal et al., 2017).

Figure 2.7: SECA mBCA 515 Multi-Frequency Body Composition Analyzer (Seca, Hamburg)



Bioimpedance analysis protocol

Contraindications to BIA were checked as follows:

- Electronic implants (e.g. cardiac pacemaker)
- Electronic prostheses
- Electronic life-support systems connected (e.g. artificial lung/ heart)
- Portable electronic medical devices

1. After height was assessed, the participant remained in their bare feet. They were asked to ensure their pockets were empty and to remove any heavy jewellery or clothing.
2. The device was pre-programmed to account for clothing by subtracting 0.5kg from weight measured.
3. The participant was instructed to stand on the machine ensuring correct placement of their feet over the foot electrodes.
4. On the touchscreen, the following information was inputted: gender, ethnicity, activity level, age and height.
5. Following the onscreen instructions, the participant grasped the handrail electrodes whilst the device conducted the measurement.
6. At the end of the assessment, FM percentage and SMM were recorded. FM percentage was compared to age and gender specific normative values (Figure 2.7) (Riebe et al., 2018).

Figure 2.8: Normative values for fat mass percentage

Fitness Categories for Body Composition (% Body Fat) for Men by Age

		Age (year)					
%		20–29	30–39	40–49	50–59	60–69	70–79
99	Very lean[a]	4.2	7.3	9.5	11.0	11.9	13.6
95		6.4	10.3	12.9	14.8	16.2	15.5
90	Excellent	7.9	12.4	15.0	17.0	18.1	17.5
85		9.1	13.7	16.4	18.3	19.2	19.0
80		10.5	14.9	17.5	19.4	20.2	20.1
75	Good	11.5	15.9	18.5	20.2	21.0	21.0
70		12.6	16.8	19.3	21.0	21.7	21.6
65		13.8	17.7	20.1	21.7	22.4	22.3
60		14.8	18.4	20.8	22.3	23.0	22.9
55	Fair	15.8	19.2	21.4	23.0	23.6	23.7
50		16.6	20.0	22.1	23.6	24.2	24.1
45		17.5	20.7	22.8	24.2	24.9	24.7
40		18.6	21.6	23.5	24.9	25.6	25.3
35	Poor	19.7	22.4	24.2	25.6	26.4	25.8
30		20.7	23.2	24.9	26.3	27.0	26.5
25		22.0	24.1	25.7	27.1	27.9	27.1
20		23.3	25.1	26.6	28.1	28.8	28.4
15	Very poor	24.9	26.4	27.8	29.2	29.8	29.4
10		26.6	27.8	29.2	30.6	31.2	30.7
5		29.2	30.2	31.3	32.7	33.3	32.9
1		33.4	34.4	35.2	36.4	36.8	37.2
n =		1,844	10,099	15,073	9,255	2,851	522

Source: Riebe et al. (2018)

2.6.5.2 Blood pressure and vascular health

Blood pressure (BP) is defined as the pressure exerted by blood as it flows through the arteries, expressed as systolic BP (SBP) over diastolic BP (DBP) in millimetres of mercury (mmHg) (Heyward and Gibson, 2014). SBP corresponds with the pressure in the arteries during systole when the heart contracts and pumps blood away from the heart. DBP corresponds with artery recoil and a drop in pressure during diastole during the re-filling phase (Heyward and Gibson, 2014). Elevated BP is reported to be the leading cause of global mortality (Unger et al., 2020). Hypertension is diagnosed as SBP ≥140 mmHg and/or DBP ≥90 mmHg, following repeated examination (Unger et al., 2020). Recent guidance from the American Heart Association has classified a SBP of 130–139 mmHg and/or DBP of 85–89 mmHg as “high-normal” (Unger et al., 2020).

Increased central aortic arterial stiffness (AS) is a common feature of ageing and arterial wall insult (Zieman et al., 2005). AS has been recognised as an independent predictor of cardiovascular disease and mortality, and as a key biomarker of vascular health (Zieman et al., 2005, DeLoach and Townsend, 2008, Segers et al., 2020). Increased AS may manifest via clinical surrogate markers of increased SBP and pulse pressure (i.e. the difference between SBP and DBP) (Zieman et al., 2005). Pulse wave velocity (PWV) is the accepted reference measurement of central AS, defined as the speed at which the arterial pulse is transmitted along the arterial wall (Segers et al., 2020). Another measurement of AS is the augmentation index (AIx), which measures the reflected pressure wave

on the aortic pressure wave form, thus representing a measure of combined aortic and peripheral arterial stiffness (Kelly et al., 1989, Izzard and Grassi, 2007). Criterion assessment methods for aortic PWV involve direct invasive measurement using pressure catheter recordings. Non-invasive direct measurement using MRI is also considered a criterion method of aortic PWV (Segers et al., 2020). When aortic PWV is not feasible, carotid-femoral PWV has been recommended as a reference standard which offers a plausible proxy measurement of AS (Segers et al., 2020). Carotid-femoral PWV may be directly measured using 2-dimensional ultrasound, however specialised equipment and expertise are required to conduct these assessments, making them less feasible for routine assessment.

An estimate of PWV can be measured indirectly using single-brachial cuff pressure devices (Butlin and Qasem, 2017, Segers et al., 2020). The device used to measure BP and AS in this project was a combined BP and pulse wave analysis (PWA) monitor, the Mobil-O-Graph® PWA (IEM GmbH, Stolberg, Germany) and its accompanying software (HMS-CS analysis software, IEM GmbH, Stolberg, Germany) (Figure 2.8). As well as brachial BP measurements, the device uses specific algorithms and technology that provides estimates of other vascular health parameters of interest, including PWV and AIx. Brachial BP measurements of the Mobil-O-Graph have been validated against standardised auscultation methods with differences of ±2-4mmHg for both SBP and DBP (Jones et al., 2000, Wei et al., 2010, Franssen and Imholz, 2010). Measures of PWV and AIx have also been validated against the SphygmoCor radial tonometry device (which measures carotid-femoral PWV) (Wassertheurer et al., 2010, Weber et al., 2011, Weiss et al., 2012, Luzardo et al., 2012, Sarafidis et al., 2014), MRI (Feistritzer et al., 2015) and intra-arterial catheterisation (Weber et al., 2011, Hametner et al., 2013). The Mobil-O-Graph has demonstrated acceptable levels of agreement with these measures, however, it was found to slightly underestimate PWV compared to radial tonometry (Luzardo et al., 2012, Sarafidis et al., 2014).

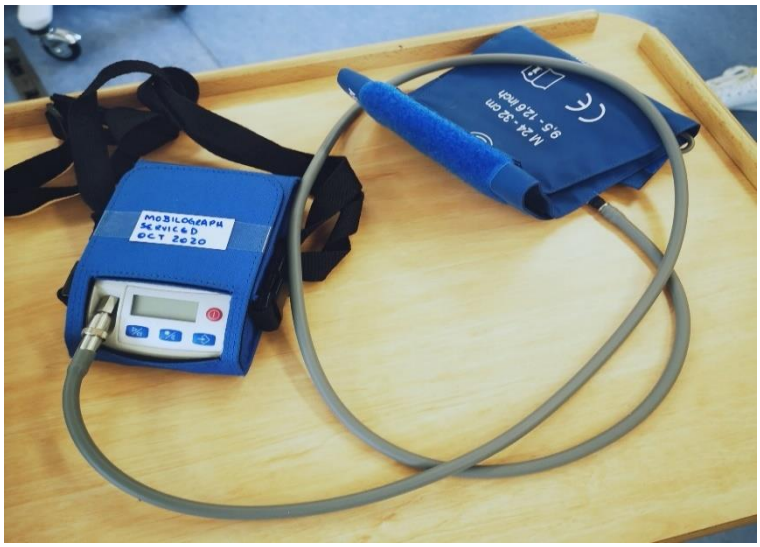
Blood pressure and arterial stiffness measurement protocol

Procedures for measurement were followed according to the device manual (Mobil-O-Graph, 2015).

1. The participant was seated in a supportive chair with both feet touching the floor.
2. They were allowed to rest for five minutes prior to the assessment to ensure they were as relaxed as possible. They were also asked to refrain from speaking or moving their arm during the measurement.
3. An appropriate BP cuff size was selected for the participant (i.e. 80% coverage of the upper arm surface area, without sliding down).
4. The cuff was placed over the brachial artery approximately 2 cm above the elbow crease-line.
5. A profile containing the participant's age, gender, weight, height and smoking status was created prior to measurement.
6. The device conducted two separate measurements with a 30 second rest in between.

7. The following vascular health parameters were recorded: SBP, DBP, HR, PWV, AIx and vascular age. BP was classified according to recommended guidelines (Unger et al., 2020). If participants were found to be hyper- or hypotensive, their BP was re-checked. If abnormal readings were still present, appropriate medical follow-up was facilitated for the participant.

Figure 2.9: The Mobil-O-Graph® PWA (IEM GmbH, Stolberg, Germany)



2.6.6 Questionnaires

A number of questionnaires were used to obtain qualitative information about various aspects of PA and quality of life (QoL) in study participants. This included information about barriers to PA, pain and functional disability.

2.6.6.1 The Patient Reported Outcomes Burdens and Experiences Questionnaire

The Patient Reported Outcomes Burdens and Experiences (PROBE) Questionnaire was used to examine various domains of patient reported outcomes and QoL in PwMSH (Appendix XIV). The PROBE was developed by people with haemophilia, for people with haemophilia, using direct patient involvement in the design, conduct, analysis and reporting of relevant patient-centred outcomes (Skinner et al., 2018). The PROBE consists of 29 questions related to patient reported outcomes, including problems with health, bleeds, joint health, mobility, pain (medications, acute, chronic) and function, amongst others (Skinner et al., 2018). The PROBE possesses good internal consistency (Cronbach's alpha= .84) and moderate to strong correlations for convergent validity (.42-.67) with the EuroQol five dimension five level instrument (EQ-5D-5L) (Chai-Adisaksopha et al., 2018). Furthermore, it has demonstrated known groups validity between individuals with and without a bleeding disorder, and individuals with a significantly more severe clinical phenotype (Chai-

Adisaksopha et al., 2018). Moderate to excellent levels of agreement for test-retest reliability (Cohen's Kappa .5-1.0) have also been demonstrated (Chai-Adisaksopha et al., 2019).

2.6.6.2 The Barriers to Being Active Quiz

The Barriers to Being Active Quiz (BBAQ) was formulated by the Centre for Disease Control and Prevention (CDC) to aid individuals and clinicians in identifying barriers to PA and inform strategies that promote PA participation (CDC, 2013). The BBAQ includes 21 items that assess the participants' perception of common internal and external barriers associated with PA engagement, including the following: Lack of time; lack of energy; lack of skill; lack of resources; lack of willpower; social influence; and fear of injury (Appendix XV). The participant is asked to rate themselves using a 4-point Likert scale (ranging from 0-3 i.e. "very unlikely" to "very likely") in relation to a series of statements about barriers to PA, with a maximum possible score of nine for each barrier domain (CDC, 2013). Aggregated scores ≥5 for each domain are considered a "critical barrier" for the participant to overcome (CDC, 2013, Zalewski et al., 2014). The BBAQ is useful in identifying general barriers to PA, however it is not disease specific. The National Hemophilia Foundation recommend its use for identifying barriers to PA in their 'Playing it Safe' guidelines for people with bleeding disorders (Anderson and Forsyth, 2017). It has previously been used in studies of sedentary adults, older community dwelling adults and students (Sawchuk et al., 2011, Kulavic et al., 2013, Zalewski et al., 2014). Moderate to strong internal consistency of the BBAQ in an elderly population has been demonstrated (Cronbach's alpha=.92 for all 21 items, .43-.85 for individual domains) (Zalewski et al., 2014). A haemophilia-specific questionnaire on barriers to PA does not currently exist, therefore the BBAQ was selected to provide an indication of potential barriers to PA faced by PwMSH, with a view to potentially building on findings in future qualitative research.

2.6.6.3 Longitudinal Follow-Up Questionnaire

A longitudinal follow-up questionnaire was designed to assess various aspects of PA and QoL in PwMSH for Study IV (Appendix XVI). This questionnaire included the Modifiable Activity Questionnaire (see section 2.6.3.2), as well as additional questions in relation to awareness and desires for PA since participation in the original research assessment in Study I. The impact of the Covid-19 pandemic on PA and QoL was also explored. This questionnaire was designed by the research team, however formal validation or prior trialling of the questionnaire in study participants was not feasible within the remaining timeframe of the project.

2.7 Data management

2.7.1 Data storage and access

All study data were pseudonymised using a study ID code. Data were stored on an encrypted electronic database on a password protected computer, only accessible to the researcher. An electronic copy of the study ID log was stored on a password protected database. A hard copy of the study ID log was locked in a cabinet stored in a secure, locked office in the hospital. Consent forms

for patients were stored in their medical chart. Consent forms for control participants were stored in a locked cabinet, in a secure, locked office. Data will be stored for a total of 10 years to allow sufficient time for project analyses and potential publication of the research findings. It will then be destroyed appropriately in accordance with institution procedures.

2.7.2 Participant feedback reports

Each study participant received a health and fitness report upon completion of their assessment (Appendix XVII). If any medical issues arose during the assessment, such as high BP, a letter explaining the issue was provided to the participant, and they were advised to follow-up with their General Practitioner.

Chapter 3: Study I: Physical activity and clinical phenotype in adults with moderate and severe haemophilia

Publication: Kennedy, M., Roche S., McGowan M., Singleton E., Elsheikh E., O'Donovan M., Ryan, K., O'Connell, N.M., O'Mahony, B., Lavin, M., O'Donnell, J.S., Turecek, P.L., Gormley, J. Physical activity, physical fitness and cardiometabolic risk amongst adults with moderate and severe haemophilia. Haemophilia. 2022; 1- 12.

3.1 Introduction

Physical activity (PA), particularly of a vigorous intensity, declines with age in the general population due to both biological and non-biological factors (Sallis, 2000). In addition to a natural age-related decline in PA throughout the life course, ageing people with moderate and severe haemophilia (PwMSH) may be less physically active than the general population. This may be due to spontaneous or trauma-induced bleeding, predominantly into joints (haemarthroses) and muscles (Mannucci and Tuddenham, 2001). Ultimately, repetitive haemarthroses result in painful, debilitating haemophilic arthropathy, which significantly impacts physical functioning and quality of life (Mancuso et al., 2021).

In recent decades, the risk of bleeding has markedly reduced in people with severe haemophilia due to prophylactic treatment with intravenously administered replacement clotting factor concentrates (Manco-Johnson et al., 2017b). A correlation between endogenous factor levels and the severity of bleeding phenotype has been established, however inter-individual variation in bleeding phenotype exists in approximately 10% of people with severe haemophilia (Rehill et al., 2021). This may be influenced by numerous factors including genetic mutations, variation in haemostatic pathways, pharmacokinetics of recombinant factor, type of haemophilia (A versus B), age of first bleeding episode, age at which prophylactic treatment was commenced, treatment regimen adherence, as well as body composition and PA (van den Berg et al., 2007, Schrijvers et al., 2016, Franchini and Mannucci, 2017, Franchini and Mannucci, 2018, Rehill et al., 2021). Despite improvements in treatment and comprehensive care in recent decades, including the development of novel therapies such as gene therapy and non-factor replacement products, bleeds and haemophilic arthropathy continue to impact PA participation in PwMSH, which may also in turn potentially influence chronic health risk. Furthermore, comorbid hepatitis C virus (HCV) and human immunodeficiency virus (HIV), acquired through contaminated treatment products in the 1970s, may pose an additional burden on quality of life and PA in affected PwMSH (Witkop et al., 2016). This is particularly relevant in light of the improved treatments for these comorbidities in recent decades and the increased life expectancy of the global haemophilia population (Darby et al., 2007, Kempton et al., 2021).

People with haemophilia were previously discouraged from partaking in PA and exercise due to the perceived risk of bleeding and joint damage. However, improved treatment options available to the haemophilia population in recent decades, particularly amongst developed nations, have shifted guidance towards PA promotion and participation (Gomis et al., 2009, Strike et al., 2016, Manco-

Johnson et al., 2017b). Despite PA being strongly recommended for people with haemophilia (Negrier et al., 2013, Srivastava et al., 2020), a consensus on the optimal volume, intensity and type of PA that is safe for individuals (i.e. does not increase the risk of bleeding) is lacking. Types of PA have been risk stratified by the National Hemophilia Foundation according to the likelihood of impact or collision (Anderson and Forsyth, 2017). Estimations of minimum and ideal factor levels for participating in activities according to these risk categories have also been proposed (Martin et al., 2020). These are general guidelines however, and the impact of individual factors that may influence bleeding risk during PA remains unknown.

The systematic review undertaken for this thesis demonstrated that the measurement of PA amongst people with haemophilia has become common over the past two decades (Chapter 1) (Kennedy et al. 2021). PA varied amongst heterogeneous samples of people with haemophilia, and was measured using a variety of PA assessment tools. The majority of studies used retrospective, self-reported measurement tools of PA. A lack of objective methods used to measure PA in the adult population with haemophilia was particularly evident. Additionally, robust reporting of bleeds and details of haemophilia treatment were lacking, making it difficult to elucidate any relationship between bleeding phenotype and PA. The following study aimed to assess PA in adult PwMSH using combined objective and subjective methods, as well as to undertake a more detailed examination of the relationship between PA and clinical phenotypic features of moderate and severe haemophilia.

3.1.1 Aim

The primary aim of this study is to determine PA participation in adult PwMSH. The secondary aim is to determine the relationship between PA and clinical phenotypic parameters.

3.1.2 Objectives

3.1.2.1 Primary objectives

1) To compare the intensity and volume of PA undertaken by adult PwMSH and adults without haemophilia using accelerometry.

2) To compare the type and self-reported volume of PA undertaken by adult PwMSH and adults without haemophilia using a questionnaire.

3) To determine retrospective PA and sports participation during childhood in adult PwMSH and adults without haemophilia.

4) To determine whether additional prophylactic treatment is used by adult PwMSH prior to engaging in PA or sport.

3.1.2.2 Secondary objectives

1) To determine the relationship between PA and age.

2) To determine the relationship between PA and bleeding phenotype, joint health and treatment regimen parameters.

3) To determine the relationship between PA and comorbid HCV and/ or HIV.

3.2 Methodology

3.2.1 Ethics, study design and setting **(See sections 2.2-2.4)**

Recruitment and data collection for this cross-sectional study was conducted between April 2018 and March 2020. PwMSH were recruited for the haemophilia group (HG) from the national haemophilia database at the National Coagulation Centre, St. James's Hospital, Dublin. Adults without haemophilia for the control group (CG) were recruited from the staff and student populations of St. James's Hospital, Trinity College Dublin and Tallaght University Hospital. Convenience sampling methods were used for both cohorts. Research assessments were carried out at the Clinical Research Facility, St. James's Hospital. This research was conducted in accordance with guidelines outlined by the Declaration of Helsinki (WMA, 2013). Ethical approval for this project was obtained from the St. James's Hospital/ Tallaght University Hospital Joint Research Ethics Committee (Appendix IV).

3.2.2 Participants and recruitment **(See section 2.5)**

Patients with haemophilia were screened for eligibility by the clinical research team during routine outpatient clinics. Males ≥18 years, with a clinical diagnosis of moderate (1-5%) or severe (<1%) Factor VIII deficiency [Haemophilia A (HA)] or Factor IX deficiency [Haemophilia B (HB)] were eligible. Individuals with active inhibitors, who lacked capacity to provide consent, who were non-ambulatory, had acute medical issues or recent, non-resolved bleeds were not eligible for this study. Healthy male volunteers ≥18 years without haemophilia or acute, unstable medical issues were invited to participate via an email and poster recruitment campaign. Individuals with neuro-musculoskeletal disorders, HCV, HIV or who lacked the ability to provide consent were not eligible. Individuals who expressed interest were screened for eligibility by the researcher. All individuals who expressed interest in partaking were provided with the relevant Participant Information Leaflet (Appendix VIII). They were contacted one week later to determine study uptake and schedule the assessment. Informed, written consent was obtained (Appendix IV).

3.2.3 Demographics and outcome measures

3.2.3.1 Demographic information

Age was recorded for both groups. The following details were obtained for participants with haemophilia from the clinical database: Haemophilia type and severity; treatment regimen and product type; inhibitor history; HCV history; HIV history; history of orthopaedic surgery. The age at which prophylaxis was commenced was also obtained using a questionnaire, where applicable.

3.2.3.2 Outcome measures

The following measures were taken according to procedures outlined in Chapter 2:

- ***Height, weight and BMI*** (See section 2.6.5.1)
- Bleeding phenotype was measured using the ***Annualised Bleeding Rate (ABR)*** (See section 2.6.2.1)
- Joint health was measured using the ***Haemophilia Joint Health Score (HJHS)*** (See section 2.6.2.2)
- PA was objectively measured over one week using the ***ActiGraph GT3X-BT accelerometer (ActiGraph Corp, Pensacola, Florida, USA)*** (See section 2.6.3.1). Raw data were downloaded cleaned and analysed using the ActiLife software. PA was classified according to achievement of PA guidelines via the total amount of MVPA undertaken per week, as well as MVPA achieved via Freedson bouts (i.e. bouts of MVPA lasting ≥10 minutes) (Bull et al., 2020).
- Types of PA undertaken during adulthood and childhood, as well as self-reported PA volume during adulthood, were measured using the ***Modifiable Activity Questionnaire*** (See section 2.6.3.2)

3.2.4 Statistical methods

Statistical analysis was undertaken using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.). Normality of the data was assessed using a combination of the Shapiro-Wilk test and a visual assessment of histograms, normal Q-Q plots and box and whisker plots. Continuous variables are described as mean ± standard deviation, and median and interquartile range (IQR: Q1, Q3). Data were skewed, therefore the Mann-Whitney U test was used to compare differences in continuous variables between two groups. In order to interpret the Mann-Whitney U test correctly, the shape of the data distribution in each group was inspected (Laerd, 2015a). A requirement of the Mann-Whitney U test is that the shape of the distribution of data in both groups of the independent variable must be inspected in order to determine how results of the test should be interpreted and reported (Laerd, 2015a). The shape of data distributions between groups differed, therefore as recommended, mean ranks are reported (Laerd, 2015a). The Kruskal-Wallis H test was used to compare continuous data between more than two groups. Dunn's post hoc pairwise comparisons were generated for the Kruskal-Wallis H test where results were statistically significant. Moderate HA and HB were grouped together as one category due to the limited sample sizes of these groups. Differences in continuous variables were examined between the study groups (HG vs. CG), and between groups of haemophilia type and severity (severe HA vs. severe HB vs. moderate HA/HB). Age, HCV and HIV statuses were considered confounding variables which could potentially impact PA, therefore continuous variables were also examined by age (<45 vs. ≥45 years), HCV history (previous history and treated successfully vs. no history) and HIV history (positive vs. negative).

Categorical data are described using frequencies and percentages. Chi-square tests of association were carried out between categorical variables. Fisher's exact test statistic is reported where expected cell counts were less than five. Weekly PA was categorised according to the achievement of PA guidelines in both the total duration of MVPA and the duration of MVPA achieved via Freedson bouts (i.e. sustained bouts of ≥10 minutes). Guidelines recommend that adults should undertake 150-300 minutes per week of moderate intensity PA, or 75-150 minutes per week of vigorous intensity PA, or an equivalent combination of both (Bull et al., 2020).

The strength and direction of association between continuous variables were examined using Spearman's rank correlation analysis (r_s) due to the skewed distribution of the data. The strength of correlations were defined as follows: 0-.10 (Negligible); .10-.39 (Weak); .40-.69 (Moderate); .70-.89 (Strong); .90-1.00 (Very strong) (Schober et al., 2018). Simple linear regression was also examined to ascertain if a predictive relationship existed between MVPA and clinical phenotypic parameters (ABR, HJHS and age at which prophylaxis was commenced). Post hoc analyses of regression models were undertaken if outliers were present, if the distribution of residuals was skewed or if the assumption of homogeneity of variance was violated. Where applicable, outliers were removed and square root transformations were applied to resolve statistical assumption violations. Square root transformations are recommended if data have a positive skew and many zero values (IBM, 2020a). Regression findings both including and excluding outliers, and/ or transformations, are reported as recommended, to allow a transparent interpretation of findings (Kirkwood and Sterne, 2003). Missing data were excluded from analyses and are highlighted throughout the text, tables and figures as appropriate with accompanying reasons. Statistical significance was taken at the level of alpha (α)= .05 (two-tailed). Where p=.000, it is implied that p is <.0005 as per the SPSS definition (IBM, 2020b)**.**

3.3 Results

3.3.1 Recruitment flow

Overall, 91 PwMSH were invited to participate in this study, and 54 were enrolled. For the control arm, 62 volunteers without haemophilia expressed interest in participating, and 33 were enrolled. Full sample descriptive statistics are presented in Appendix XVIII. Participants who did not complete the ActiGraph assessment or meet ActiGraph wear-time inclusion criteria (≥10 hours on 4 days, including one weekend day; See section 2.6.3.1) were excluded from the analysis. A final sample of 78 participants, which consisted of 48 participants in the HG and 30 in the CG, was analysed. Recruitment flow charts including reasons for non-inclusion or non-participation are provided in Figures 3.1a and 3.1b.

Figure 3.1a: Recruitment flow chart (haemophilia group)

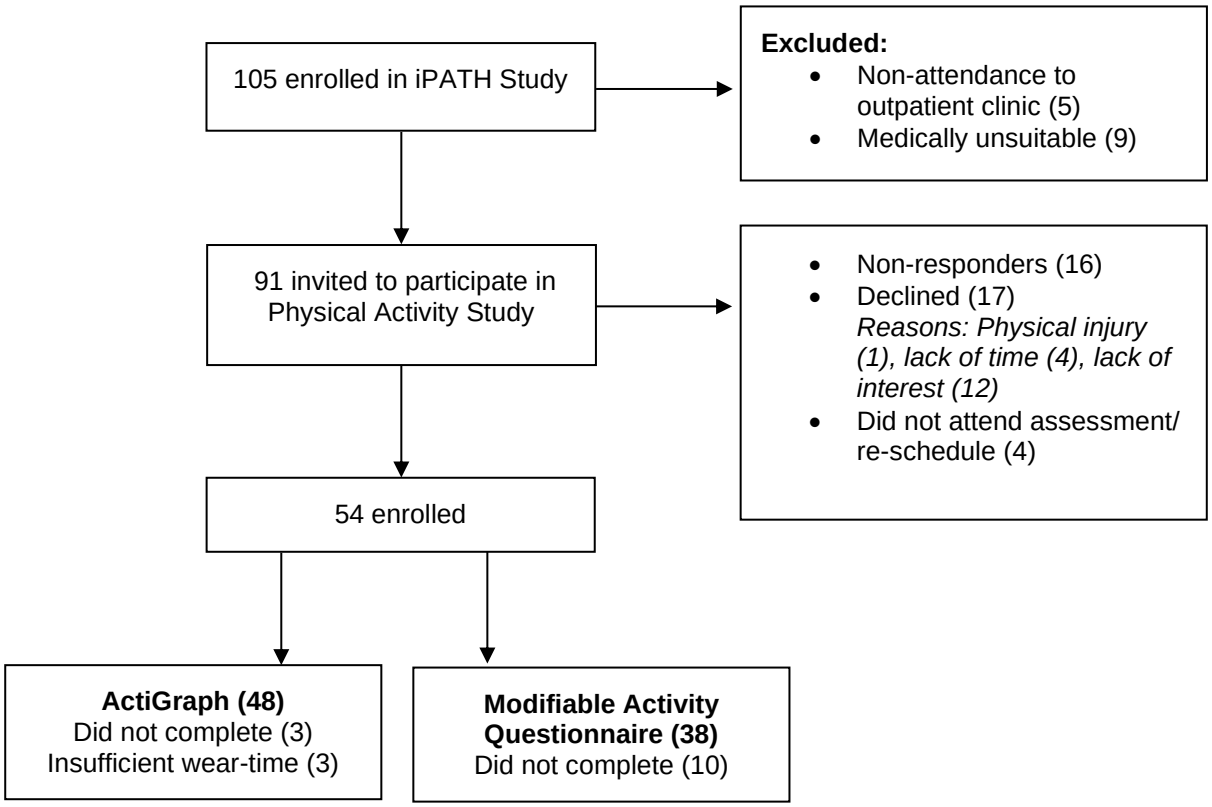
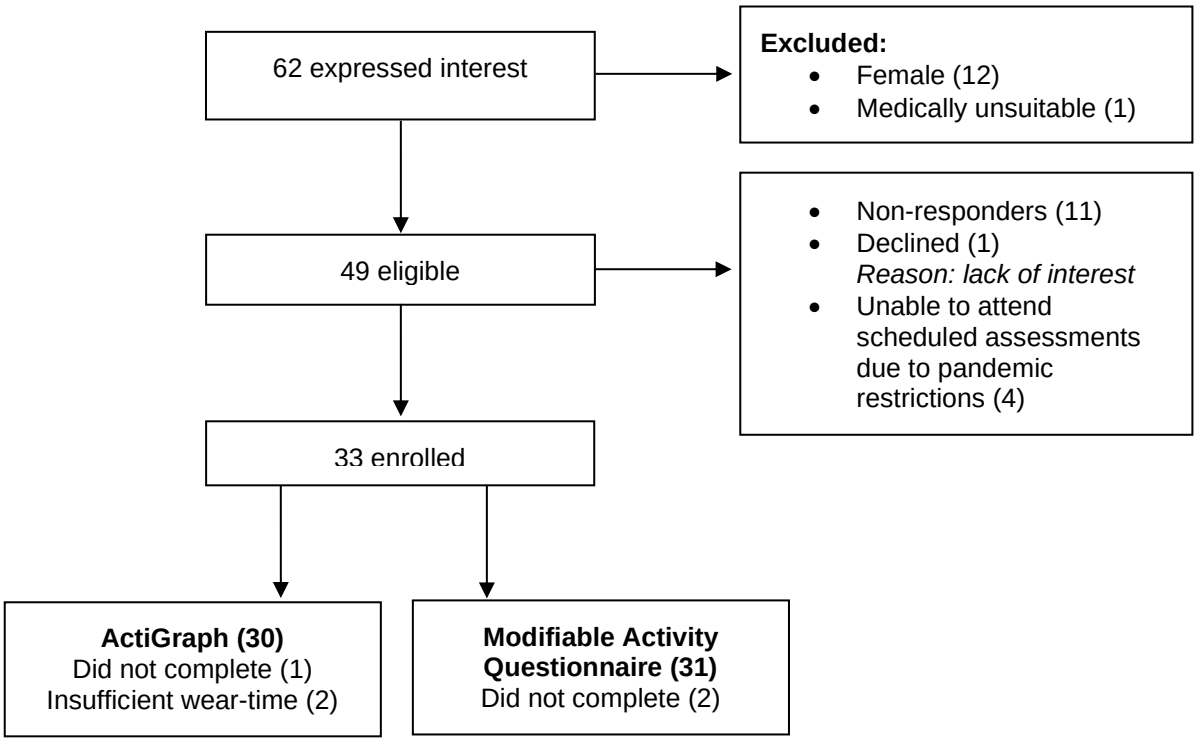


Figure 3.1b: Recruitment flow chart (control group)



3.3.2 Demographics and clinical phenotype

3.3.2.1 Demographic information

Demographics of both study groups are presented throughout Tables 3.1a-3.1c. The median age of both groups was 44 years. There were no significant differences between the HG and CG, or within the HG, for age or anthropometry. In the HG, 54.2% had severe HA, 31.2% had severe HB, 12.5% had moderate HA and 2.1% had moderate HB. All participants with severe haemophilia and one participant with moderate HA were treated with prophylaxis (87.5%), whilst the remaining participants who had moderate haemophilia were treated on demand (12.5%). The overall mean age at which participants commenced prophylaxis was 29 ± 19 [median= 26; IQR (13, 49)] years. There was no significant difference in the age at which prophylaxis was commenced between participants with HA or HB who were treated with prophylaxis [mean ranks= 17.25 vs. 22.23 (respectively); U= 198.0; p=.189], and age was strongly correlated with the age at which prophylaxis was commenced (r_s= .885; p= .000). A previous history of inhibitors was present in 12.5%, whilst the remaining 87.5% had no history. With regard to comorbidities acquired through contaminated treatment products, 72.9% had been treated for HCV, and 27.1% were HIV positive. Overall, 31.3% had undergone orthopaedic joint replacement surgery.

3.3.2.2 Prophylactic treatment products

Extended half-life factor (EHL) products were used by 90.5% of participants at the time of the research assessment. During the previous year of the study period, participants with severe HA who were treated with prophylaxis were in the process of switching from a standard half-life factor (SHL) product to an EHL product. Therefore, some participants were on a SHL product for part of the previous year before their research assessment. Two adults with severe HA and four adults with severe HB had not yet switched to an EHL product by the time of their research assessment. Participants with HB treated with an EHL product for significantly longer prior to their research assessment compared to participants with HA [mean ranks= 30.13 vs. 14.72 (respectively); U= 332.0; p=.000]. Similarly, participants with HA treated with a SHL product for significantly longer prior to their research assessment compared to participants with HB [mean ranks= 26.86 vs. 9.90 (respectively); U= 28.5; p=.000].

3.3.2.3 Joint health

The total HJHS and its individual component scores are broken down by type and severity of haemophilia in Table 3.3.2b. The overall HJHS of the group was 27 ± 13 [27 (20, 34)]. Upon further inspection of individual joint component scores of the upper and lower limbs, the ankles were the most severely affected joint [11 ± 6; 12 (7, 15)], followed by the elbows [7 ± 6; 7 (1, 12)] and knees [5 ± 5; 4 (0, 9)]. The mean global gait component score was 4 ± 1 [4 (4, 4)]. There was no significant difference between participants with HA or HB for the total HJHS [mean ranks= 21.21 vs. 23.47

(respectively); U= 232.0; p= .574]. The HJHS was moderately correlated with age [r_s=.628; p=.000] and the age at which prophylaxis was commenced [r_s=.646; p=.000].

3.3.2.4 Bleeding phenotype

Bleeding phenotype is presented by type and severity of haemophilia in Table 3.1b. The median ABR was 2 (1, 4) bleeds per year, and the Annualised Joint Bleed Rate was 1 (0, 3) bleed per year. Clinically defined target joints (i.e. ≥ three spontaneous bleeds into one joint within the previous six months) were non-existent with a median of 0 (0, 0; total range= 0). Causes of bleeding were unknown for the majority of bleeds, accounting for a median of 1 (0, 3) bleed. Amongst participants who reported a cause of bleeding, the median number of spontaneous bleeds reported was 0 (0, 1), and the median number of traumatic bleeds reported was 0 (0, 1). Bleeds were not clinically verified or diagnosed in 79.2% of participants who reported at least one bleeding episode, with a median number of clinically verified bleeds of 0 (0, 0). No bleeding episodes were reported in 20.8% of participants over the previous year. There were no significant differences between groups of haemophilia type and severity for ABR, Annualised Joint Bleed Rate, spontaneous bleeds, traumatic bleeds or bleeds of unknown cause. Clinically verified bleeds were significantly different [H(2)= 11.118; p= .004]. Post hoc pairwise comparisons revealed that differences between severe HA and severe HB were not significant (p=.386), but there was a significantly higher number of clinically verified bleeds in participants with moderate HA/HB compared to participants with severe HA (p=.004) and severe HB (p= .001). Correlations between ABR with age and the age at which prophylaxis was commenced were negligible [r_s= .085; p= .566; r_s= -.031; p= .855, respectively].

Table 3.1a: Demographic information of the haemophilia and control groups

	HG (48)		CG (30)				
	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ranks (HG vs. CG)	U	p
Age (years)	43 ± 13	44 (33, 53)	44 ± 9	44 (37, 47)	38.85 vs. 40.53	689.0	.750
Height (cm)	175.3 ± 7.3	173.9 (169.1, 181.6)	176.2 ± 6.7	176.1 (172.0, 180.9)	37.92 vs. 42.03	644.0	.435
Weight (kg)	84.0 ± 16.6	83.8 (71.6, 94.1)	82.4 ± 11.7	83.2 (73.7, 87.8)	40.41 vs. 38.05	763.5	.655
Body Mass Index (kg/m^2)	27.3 ± 4.8	27.4 (24.8, 30.6)	26.6 ± 4.0	25.2 (24.0, 28.8)	41.61 vs. 36.12	821.5	.297

Values are presented as mean ± standard deviation and median (Q1, Q3); Groups compared using the Mann-Whitney U test; α= .05 (two-tailed).

Table 3.1b: Demographic and clinical phenotypic information by type and severity of haemophilia (continuous variables)

	Severe HA (26)		Severe HB (15)		Moderate HA (6)		Moderate HB (1)		
	Mean ± SD	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Raw data**	**H**	**p**
Age (years)	40 ± 13	39 (29, 50)	47 ± 13	47 (42, 55)	47 ± 13	50 (33, 59)	32	3.001	.223
Age prophylaxis commenced (years)†	27 ± 20	23 (12, 48)	34 ± 18	38 (20, 51	7 (raw data)		-	-	-
Anthropometry									
Height (cm)	175.0 ± 7.2	175.4 (168.3, 181.7)	174.0 ± 5.0	172.4 (169.3, 176.8)	177.3 ± 11.1	175.9 (167.2, 187.0)	189.0	.851	.653
Weight (kg)	84.0 ± 19.7	81.7 (68.9, 98.8)	83.0 ± 12.4	84.0 (75.9, 89.7)	85.4 ± 12.4	88.8 (71.9, 95.0)	103.0	1.057	.590
Body Mass Index (kg/m^2)	27.1 ± 5.3	26.9 (22.4; 30.8)	27.5 ± 4.0	28.3 (24.9; 30.6)	27.4 ± 5.5	25.8 (23.7, 33.8)	28.8	.238	.888
Joint Health‡									
HJHS Total	27 ± 13	29 (21, 36)	28 ± 14	27 (21, 34)	17 & 7 (raw data)		-	-	-
HJHS Elbow	8 ± 6	8 (4, 13)	6 ± 5	6 (1, 9)	1 & 0 (raw data)		-	-	-
HJHS Knee	5 ± 5	4 (0, 7)	6 ± 6	4 (2, 10)	5 & 1 (raw data)		-	-	-
HJHS Ankle	10 ± 6	12 (6, 14)	12 ± 5	12 (10, 15)	7 & 2 (raw data)		-	-	-
Global Gait Score	3 ± 1	4 (4, 4)	4 ± 1	4 (4, 4)	4 & 4 (raw data)		-	-	-
Bleeding phenotype									
ABR (Bleeds per year)	3 ± 3	2 (1, 3)	3 ± 4	2 (1, 4)	4 ± 3	4 (2, 7)	0	.926	.629
AJBR (Joint bleeds per year)	2 ± 2	1 (0, 2)	2 ± 2	1 (0, 3)	1 ± 2	1 (0, 3)	0	.381	.826
Spontaneous bleeds	0 ± 1	0 (0, 0)	1 ± 1	0 (0, 1)	1 ± 1	2 (0, 2)	0	4.716	.701
Traumatic bleeds	1 ± 1	0 (0, 1)	1 ± 1	1 (0, 1)	1 ± 1	1 (0, 2)	0	3.469	.176
Unknown cause bleeds	2 ± 3	1 (0, 3)	2 ± 3	0 (0, 3)	2 ± 3	1 (0, 4)	0	.710	.701
Clinically defined target joints	0 ± 0	0 (0, 0)	0 ± 0	0 (0, 0)	0 ± 0	0 (0, 0)	0	-	-
Clinically verified bleeds§	0 ± 1	0 (0, 0)	0 ± 0	0 (0, 0)	2 ± 2	1 (1, 4)	0	11.118	**.004***
Number of days on treatment products									
Extended half-life product	163.9 ± 171.6	122.0 (34.5, 223.0)	436.0 ± 80.7	441.0 (364.0, 476.0)	555 (raw data)		-	-	-
Standard half-life product	228.6 ± 119.0	243.0 (142.0, 330.5)	3.5 ± 7.5	0 (0, 1.0)	-		-	-	-
Non-factor product	371 & 491 (raw data)		-	-	-		-	-	-

Values are presented as mean ± standard deviation and median (Q1, Q3); Raw values are presented where n= 1 or 2; ABR Annualised Bleeding Rate **AJBR** Annualised Joint Bleeding Rate **HA** Haemophilia A **HB** Haemophilia B **HJHS** Haemophilia Joint Health Score; **Groups compared using the Kruskal-Wallis H test**; **†** n= 37 (Severe HA= 23; Severe HB= 13; Moderate HA=1; Not applicable to 6 participants with moderate haemophilia; 5 participants with severe haemophilia did not answer question); **‡** n= 43 (not available for 5 participants with moderate haemophilia); **§** n= 38 who reported bleeds**; *statistically significant at α= .05 (two-tailed).**

Table 3.1c: Demographic and clinical phenotypic information by type and severity of haemophilia (categorical variables)

	Total	Severe HA	Severe HB	Moderate HA	Moderate HB
	n (%)	n (%)	n (%)	n (%)	n (%)
N	48 (100)	26 (54.2)	15 (31.2)	6 (12.5)	1 (2.1)
Inhibitor history					
History of inhibitors (non-active)	6 (12.5)	5 (83.3)	1 (16.7)	0	0
No history of inhibitors	42 (87.5)	21 (50.0)	14 (33.3)	6 (14.3)	1 (2.4)
Treatment regimen					
On demand	6 (12.5)	-	-	5 (83.3)	1 (16.7)
Prophylaxis	42 (87.5)	26 (61.9)	15 (35.7)	1 (2.4)	-
Treatment product					
Standard half-life product	2 (4.8)	2 (100)	0	-	-
Extended half-life product	38 (90.4)	22 (57.9)	15 (39.5)	1 (2.6)	-
Non-factor product	2 (4.8)	2 (100)	-	-	-
History of chronic infectious disease					
HCV (previous history)	35 (72.9)	16 (45.7)	14 (40.0)	5 (14.3)	0
HCV (no previous history)	13 (27.1)	10 (76.9)	1 (7.7)	1 (7.7)	1 (7.7)
HIV (positive)	12 (25.0)	9 (75.0)	1 (8.3)	2 (16.7)	0
HIV (negative)	36 (75.0)	17 (47.2)	14 (38.9)	4 (11.1)	1 (2.8)
Orthopaedic surgical history					
Ankle arthrodesis	7 (14.6)	3 (42.9)	4 (57.1)	0	0
Total knee replacement	6 (12.5)	4 (66.7)	2 (33.3)	0	0
Total elbow replacement	1 (2.1)	1 (100)	0	0	0
Total hip replacement	1 (2.1)	0	1 (100)	0	0

Values are presented as n (%); HA Haemophilia A **HB** Haemophilia B **HCV** Hepatitis C Virus **HIV** Human Immunodeficiency Virus

3.3.3 Physical Activity

3.3.3.1 Objective physical activity

Objective PA parameters are presented for the total HG and CG in Table 3.2a. There were no significant differences between the HG and CG for light PA or minimum duration of time spent in Freedson bouts. The CG were significantly more active than the HG for all parameters of MVPA. PA guideline recommendations of at least 150 minutes per week of moderate PA, were met by 72.9% of the HG and 90% of the CG [$\chi 2(1) = 3.304$; p=.069; Fisher's exact= .088]. When analysed according to MVPA achieved via Freedson bouts, 18.8% of the HG met guidelines compared to 56.7% in the CG [$\chi 2(1) = 11.944$; p=.001; Fisher's exact= .001]. The number of weekdays and weekend days with valid ActiGraph wear-time were similar between the HG and CG. Despite a similar duration of wear-time on valid days between and the HG and the CG, differences were statistically significant. Objective PA data are presented by type and severity of haemophilia in Table 3.2b. Wear-time was similar between groups, and there were no significant differences between groups in any parameter of PA.

3.3.3.2 Self-reported physical activity

The Modifiable Activity Questionnaire was completed by 38 participants in the HG, and 31 in the CG. The mean duration per month of self-reported MVPA was 1713.2 ± 1890.8 (median= 1020.0) minutes per month in the HG, and 2037.0 ± 1519.8 (median= 1877.5) minutes per month in the CG. Self-reported MVPA was not significantly different between the HG and CG [mean ranks= 27.71 vs. 34.88 (respectively); U= 353.5; p= .116]. Participation in various types of PA and sport, including details of self-reported frequency (the number of months per year and the number of times per month) and duration of activity (on each occasion), are presented in Table 3.3a. The most popular types of PA in both groups included walking, cycling, swimming, gardening and weight training. A variety of other types of PA and sport were undertaken by the HG, including high risk collision activities, such as soccer, hurling, Gaelic football and boxing. Self-reported frequency and duration of the most popular activities in both groups are presented in Table 3.3b. The number of months per annum spent doing all activities listed were comparable. The HG reported a significantly higher frequency of walking, weight training and gym attendance per month, compared to the CG. The CG reported a significantly higher frequency of cycling per month, and a significantly longer duration in walking, compared to the HG. The remaining activities were not significantly different between groups for monthly frequency or duration on each occasion.

Participants with haemophilia who were treated with prophylaxis were asked whether they took additional prophylaxis prior to engaging in PA or sport. Of 33 participants who answered this question, 9.1% reported they did take additional prophylaxis for PA or sport, whilst the remaining 90.9% reported they did not.

Participants in both groups were also asked if they participated in PA or sport during childhood, and results are presented in Table 3.3c. Of 34 participants in the HG who answered, 58.8% reported they

did participate in PA or sport as a child, whilst 41.2% reported they did not. Of 29 participants in the CG, 93.1% reported they participated in PA or sport as a child, compared to 6.9% who did not. Childhood PA or sports participation was significantly different between the two study groups [n=63; $\chi 2(1) = 9.707$; p=.002; Fisher's exact= .003]. A variety of contact and non-contact sports and activities were played during childhood amongst both groups, with soccer, hurling and swimming being the most popular sports. Additional qualitative information describing reasons for PA participation or non-participation during childhood was provided by a number of participants, and details are presented in Table 3.3d. Amongst those who did not participate in PA, reasons included a lack of permission, fear of bleeds and fear of joint damage. Amongst those who did participate in PA, they emphasised that they proceeded to do so despite being advised against it.

Table 3.2a: Objectively measured physical activity for the total HG and CG

	HG (48)		CG (30)				
	Mean ± SD	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean ranks**	**U**	**p**
Light PA (mins/wk)	2009.8 ± 677.9	1931.0 (1529.8, 2399.0)	1794.6 ± 436.3	1723.5 (1523.3, 2129.0)	42.42 vs. 34.83	860.0	.150
Moderate PA (mins/wk)	222.5 ± 137.3	196.5 (139.0, 305.0)	298.8 ± 159.0	256.0 (198.0, 421.8)	34.77 vs. 47.07	493.0	**.020***
Vigorous PA (mins/wk)	7.9 ± 23.1	0 (0, 2.0)	42.6 ± 56.0	24.5 (0, 63.5)	31.86 vs. 51.72	353.5	**.000***
MVPA (mins/wk)	230.5 ± 145.6	218.0 (139.0, 305.3)	341.4 ± 169.7	318.5 (223.3, 461.3)	33.22 vs. 49.55	418.5	**.002***
Total Freedson MVPA† (mins/wk)	82.4 ± 96.1	45.5 (11.0, 124.0)	174.8 ± 105.2	177.0 (82.5, 257.8)	31.40 vs. 52.47	331.0	**.000***
Average Freedson† (mins/wk)	13.5 ± 7.5	13.3 (11.0, 17.3)	19.3 ± 6.4	18.9 (15.4, 21.9)	32.30 vs. 51.02	374.5	**.000***
Maximum Freedson† (mins/wk)	19.2 ± 13.1	16.0 (11.0, 28.0)	38.8 ± 20.8	36.5 (26.5, 47.5)	30.64 vs. 53.68	294.5	**.000***
Minimum Freedson† (mins/wk)	9.8 ± 5.2	10.0 (10.0, 11.0)	11.3 ± 3.5	10.0 (10.0, 10.0)	40.47 vs. 37.95	766.5	.588
Valid weekdays	5.3 ± 1.0	5.0 (5.0, 6.0)	5.3 ± 1.0	5.0 (5.0, 5.3)	40.59 vs. 37.75	772.5	.552
Valid weekend days	1.8 ± .5	2.0 (1.3, 2.0)	2.0 ± .4	2.0 (2.0, 2.0)	37.06 vs. 43.40	603.0	.108
Wear-time on valid days (hours)	14.1 ± 1.3	14.1 (13.3, 14.4)	15.0 ± 1.0	15.2 (14.2, 15.6)	32.41 vs. 50.85	379.5	**.000***

Values are presented as mean ± standard deviation and median (Q1, Q3); CG Control Group **HG** Haemophilia Group **mins/wk** Minutes per week **MVPA** Moderate Vigorous Physical Activity; **† Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes; **Groups compared using the Mann-Whitney U test; *statistically significant at α= .05 (two-tailed).**

Table 3.2b: Objectively measured physical activity by type and severity of haemophilia

	Severe HA (26)		Severe HB (15)		Moderate HA (6)		Moderate HB (1)		
	Mean ± SD	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Raw data**	**H**	**p**
Light PA (mins/wk)	1978.6 ± 647.7	1882.0 (1567.3, 2413.3)	2136.0 ± 726.5	2023.0 (1489.0, 2429.0)	2002.3 ± 689.8	1898.0 (1551.0, 2573.5)	971	.891	.640
Moderate PA (mins/wk)	225.3 ± 160.1	193.0 (104.5, 314.8)	217.5 ± 94.2	224.0 (173.0, 284.0)	232.0 ± 152.9	174.5 (139.3, 329.0)	169	.498	.779
Vigorous PA (mins/wk)	7.8 ± 24.3	0 (0, 1.3)	4.3 ± 11.9	0 (0, 2.0)	2.8 ± 3.7	1.0 (0, 7.3)	97	1.535	.464
MVPA (mins/wk)	233.1 ± 173.1	203.0 (104.5, 316.3)	221.8 ± 93.9	229.0 (175.0; 285.0)	234.8 ± 156.0	175.0 (140.0, 336.3)	266	.287	.866
Total Freedson† (mins/wk)	78.9 ± 103.9	32.0 (11.0, 122.0)	67.5 ± 56.2	66.0 (12.0, 97.0)	117.5 ± 140.2	76.5 (9.8, 214.8)	185	1.410	.494
Average Freedson† (mins/wk)	13.3 ± 7.5	13.6 (11.0, 16.6)	12.9 ± 7.7	12.2 (10.5, 13.7)	14.9 ± 9.0	15.4 (9.6, 21.0)	17	1.633	.442
Maximum Freedson†(mins/wk)	19.4 ± 14.0	16.0 (11.0, 30.3)	17.5 ± 11.0	15.0 (12.0, 28.0)	22.7 ± 16.1	22.5 (9.8, 35.5)	20	.774	.679
Minimum Freedson†(mins/wk)	9.4 ± 4.5	10.0 (10.0, 11.0)	10.5 ± 6.8	10.0 (10.0, 11.0)	9.5 ± 5.0	10.0 (7.5, 13.3)	11	.199	.905
Valid weekdays	5.5 ± 1.0	5.0 (5.0, 6.0)	5.1 ± .8	5.0 (5.0, 6.0)	4.8 ± 1.0	5.0 (4.5, 5.3)	7	1.448	.485
Valid weekend days	1.8 ± .6	2.0 (1.0, 2.0)	1.9 ± .4	2.0 (2.0, 2.0)	1.7 ± .5	2.0 (1.0, 2.0)	2	.696	.706
Wear-time (hours per day)	13.8 ± .9	14.1 (13.2, 14.4)	14.5 ± 2.0	14.3 (13.3, 16.1)	14.3 ± 1.1	14.3 (13.7, 15.4)	13.2	1.909	.385

Values are presented as mean ± standard deviation and median (Q1, Q3); Raw values are presented where n= 1; HA Haemophilia A **HB** Haemophilia B **mins/wk** Minutes per week **MVPA** Moderate Vigorous Physical Activity **PA** Physical Activity; **† Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes; **Groups compared using the Kruskal-Wallis H test; *statistically significant at α= .05 (two-tailed).**

Table 3.3a: Self-reported type, frequency and duration of physical activity

Activity/ Sport	n (%)		Frequency (months per annum) Median (Q1, Q3)		Frequency (times per month) Median (Q1, Q3)		Duration (minutes each time) Median (Q1, Q3)	
	HG (38)	CG (31)	HG (38)	CG (31)	HG (38)	CG (31)	HG (38)	CG (31)
Cycling	14 (37)	19 (61)	11 (8, 12)	12 (10, 12)	5 (2, 11)	20 (7, 30)	30 (24, 68)	45 (20, 60)
Walking for exercise	29 (76)	19 (61)	12 (8, 12)†	12 (9, 12)	15 (8, 20)	8 (4, 10)	30 (30, 39)†	45 (30, 60)
Weight training	11 (29)	11 (35)	12 (6, 12)	11 (5, 12)	12 (8, 15)	8 (4, 10)	30 (20, 60)	30 (20, 60)
Gym	10 (26)	8 (26)	12 (6, 12)†	12 (8, 12)	15 (12, 20)†	9 (5, 12)	60 (30, 60)†	35 (23, 55)
Calisthenics/ Toning	1 (3)	1 (3)	6 (raw value)	12 (raw value)	5 (raw value)	3 (raw value)	15 (raw value)	15 (raw value)
Swimming	12 (32)	15 (48)	12 (4, 12)	6 (5, 12)	6 (4, 10)	4 (2, 12)	35 (23, 44)	30 (20, 60)
Hydrotherapy	4 (11)	0	12 (8, 12)	-	4 (3, 7)	-	60 (38, 60)	-
Hiking	4 (11)	5 (16)	6 (2, 10)	7 (7, 10)	2 (1, 4)	2 (1, 2)	150 (120, 270)	150 (85, 270)
Hurling	2 (5)	2 (6)	6 & 1 (raw value)	7 & 5 (raw value)	1 & 1 (raw value)	5 & 4 (raw value)	10 & 60 (raw value)	60 & 60 (raw value)
Cross-training	1 (3)	0	12 (raw value)	-	20 (raw value)	-	60 (raw value)	-
Gaelic football	1 (3)	0	4 (raw value)	-	2 (raw value)	-	20 (raw value)	-
Football/ Soccer	3 (8)	9 (29)	4 (4-12)‡	10 (5, 12)	2 (2-4)‡	4 (4, 8)	45 (20-45)‡	60 (60, 60)
Fishing	3 (8)	2 (6)	5 (5-8)‡	5 & 5 (raw value)	10 (4-18)‡	3 & 1 (raw value)	180 (120-300)‡	90 & 90 (raw value)
Golf	2 (5)	0	12 & 7 (raw value)	-	16 & 3 (raw value)	-	240 & 90 (raw value)	-
Bowling	1 (3)	0	12 (raw value)	-	3 (raw value)	-	60 (raw value)	-
Badminton	1 (3)	1 (3)	9 (raw value)	12 (raw value)	2 (raw value)	5 (raw value)	30 (raw value)	60 (raw value)
Stair master	2 (5)	1 (3)	12 & 12 (raw value)	7 (raw value)	12 & 4 (raw value)	7 (raw value)	30 & 10 (raw value)	20 (raw value)
Rowing	1 (3)	1 (3)	12 (raw value)	12 (raw value)	8 (raw value)	4 (raw value)	30 (raw value)	30 (raw value)
Table tennis	1 (3)	0	4 (raw value)	-	1 (raw value)	-	120 (raw value)	-
HIIT	2 (5)	6 (19)	6 & 12 (raw value)	11 (6, 12)†	20 & 11 (raw value)	4 (4, 12)	10 & 15 (raw value)	38 (28, 49)
Hunting	1 (3)	1 (3)	5 (raw value)	5 (raw value)	10 (raw value)	4 (raw value)	180 (raw value)	180 (raw value)

Values are presented at n (%) or median (IQR: Q1, Q3); Raw values are reported where n = 1 or 2; CG Control Group (n= 31) **HG** Haemophilia Group (n= 38) **HIIT** High Intensity Interval Training**;**
† n-1 (who did not answer)**; ‡** Values are median [range (min-max)] as IQR not applicable for n=3

Table 3.3a: Self-reported type, frequency and duration of physical activity (continued)

Activity/ Sport	n (%)		Frequency (months per annum) Median (Q1, Q3)		Frequency (times per month) Median (Q1, Q3)		Duration (minutes each time) Median (Q1, Q3)	
	HG (38)	CG (31)	HG (38)	CG (31)	HG (38)	CG (31)	HG (38)	CG (31)
Tennis	1 (3)	0	2 (raw value)	-	4 (raw value)	-	60 (raw value)	-
Boxing	1 (3)	0	5 (raw value)	-	10 (raw value)	-	90 (raw value)	-
Cricket	1 (3)	0	5 (raw value)	-	5 (raw value)	-	420 (raw value)	-
Yoga/ Pilates	1 (3)	6 (19)	9 (raw value)	6 (2, 11)	4 (raw value)	4 (3, 4)	90 (raw value)	53 (34; 41, 75)
Jogging	3 (8)	21 (68)	6 (3-12)‡	12 (10, 12)†	15 (4-20)‡	8 (5, 12)	20 (10-20)‡	30 (30, 60)
Skiing	0	4 (13)	-	1 (1, 3)	-	10 (6, 12)	-	150 (120,315)
Baseball	0	1 (3)	-	9 (raw value)	-	4 (raw value)	-	90 (raw value)
Martial arts	0	1 (3)	-	4 (raw value)	-	8 (raw value)	-	120 (raw value)
Rock climbing	0	1 (3)	-	5 (raw value)	-	2 (raw value)	-	60 (raw value)
Jump rope	0	1 (3)	-	8 (raw value)	-	4 (raw value)	-	3 (raw value)
Horseback riding	0	1 (3)	-	6 (raw value)	-	20 (raw value)	-	30 (raw value)
Cross-fit	0	1 (3)	-	12 (raw value)	-	4 (raw value)	-	45 (raw value)
Basketball	0	1 (3)	-	5 (raw value)	-	8 (raw value)	-	20 (raw value)
Gardening/ Yard work	15 (39)	10 (32)	7 (6, 12)§	6 (7; 4, 11)	4 (2, 7)¶	2 (2, 3)	30 (23, 113)¶	38 (30, 68)
Water/ Coal hauling	5 (13)	1 (3)	6 (3, 12)	7 (raw value)	4 (3, 5)	20 (raw value)	30 (23, 53)†	5 (raw value)
Wood-chopping	4 (11)	1 (3)	5 (4, 10)	7 (raw value)	4 (2, 4)	4 (raw value)	45 (20-120)†	20 (raw value)
Stair climbing	1 (3)	1 (3)	12 (raw value)	12 (raw value)	30 (raw value)	20 (raw value)	-†	20 (raw value)
Tower climbing	1 (3)	0	12 (raw value)	-	60 (raw value)	-	100 (raw value)	-

Values are presented at n (%) or median (IQR: Q1, Q3); Raw values are reported where n = 1 or 2; CG Control Group (n= 31) **HG** Haemophilia Group (n= 38)**; †** n-1 (did not answer); **‡** Values are median [range (min-max)] as IQR not applicable for n=3; **§** n-2 (did not answer)**; ¶ n-3** (did not answer)

Table 3.3b: Comparison of popular activities and sport between study groups

Activity/ Sport	n (%)		Frequency (months per annum)			Frequency (times per month)			Duration (minutes each time)		
	HG (38)	CG (31)	Mean ranks	U	p	Mean ranks	U	p	Mean ranks	U	p
Cycling	14 (37)	19 (61)	14.46 vs. 18.87	97.5	.199	12.07 vs. 20.63	64.0	**.011***	15.96 vs. 17.76	118.5	.602
Walking for exercise	29 (76)	19 (61)	22.75† vs. 25.84	231.0	.385	28.21 vs. 18.84	383.0	**.023***	20.25† vs. 29.53	161.0	**.018***
Weight training	11 (29)	11 (35)	11.82 vs. 11.18	64.0	.847	14.82 vs. 8.18	97.0	**.016***	10.77 vs. 12.23	52.5	.606
Gym	10 (26)	8 (26)	8.83† vs. 9.19	34.5	.888	11.72† vs. 5.94	60.5	**.015***	10.67† vs. 7.12	51.0	.167
Swimming	12 (32)	15 (48)	15.00 vs. 13.20	102.0	.581	15.12 vs. 13.10	103.5	.516	13.46 vs. 14.43	83.5	.755
Gardening/ Yard work	15 (39)	10 (32)	13.42‡ vs. 10.15	83.5	.257	13.50§ vs. 9.10	84.0	.123	11.17‡ vs. 11.90	56.0	.821

CG Control Group **HG** Haemophilia Group**; Groups compared using the Mann-Whitney U test; Mean ranks are presented in order of HG vs. CG; †** n-1; **‡** n-2 (did not answer); **§** n-3 (did not answer); ***statistically significant at α= .05 (two-tailed).**

Table 3.3c: Participation in childhood physical activities and sports

Type of physical activity	HG (18) n (%)	CG (26) n (%)
Gaelic football	2 (11.1)	10 (38.5)
Hurling	4 (22.2)	7 (26.9)
Swimming	6 (33.3)	4 (15.4)
Cycling	4 (22.2)	2 (7.7)
Golf	1 (5.6)	2 (7.7)
Soccer	11 (61.1)	14 (53.8)
Basketball	2 (11.1)	4 (15.4)
Jogging/ running	2 (11.1)	6 (23.1)
Tennis	3 (16.7)	2 (7.7)
Table tennis	2 (11.1)	-
Sailing or water-sports	1 (5.6)	-
Hunting	1 (5.6)	-
Fishing	1 (5.6)	-
Judo	1 (5.6)	-
Cricket	1 (5.6)	-
Climbing	1 (5.6)	-
Rugby	-	5 (19.2)
Karate	-	1 (3.8)
Weight training	-	2 (7.7)
Orienteering	-	1 (3.8)
GAA	-	2 (7.7)
Athletics	-	1 (3.8)
Horseback riding	-	1 (3.8)
Hiking	-	1 (3.8)
Gymnastics	-	1 (3.8)
Dancing	-	2 (7.7)
PE at school	-	1 (3.8)
Ball sports	-	1 (3.8)
Boxing	-	1 (3.8)

Values are presented as n (%); CG Control group (26, N-1 did not answer)**;**
HG Haemophilia group (18, N-2 did not answer)**; GAA** Gaelic Athletic Association (i.e. Gaelic football or hurling, non-specific**) PE** Physical Education

Table 3.3d: Reasons for engagement or non-engagement in childhood activity or sport

Did you play sport or do exercise as a child? (HG)	
No	**Yes**
“Due to joints”	“All the stuff I was told not to do!!”
“Due to bleeds”	“Played sport”
“No particular reason, just didn't”	“Did everything that I shouldn't have participated in being a haemophiliac e.g. soccer, BMX, etc….not at competitive level but on the street/ park, etc.”
“Wasn't allowed”	-
“Due to haemophilia”	-
“Disinterested/ bleeds”	-
“Due to possible bleeds as a child”	-
“Because of haemophilia”	-
“Due to haemophilia”	-
Did you play sport or do exercise as a child? (CG)	
No	**Yes**
“Only football available”	-
“No peer support; school had no gym or sports facilities”	-

3.3.3.3 Objective physical activity and age

An examination of the relationship between age and objective PA parameters in both study groups is presented in Table 3.4.

Table 3.4: Correlations between age and objective physical activity parameters

	HG (48): Age (years)		CG (30): Age (years)	
	r_s	p	r_s	p
Light PA (mins/wk)	.013	.931	-.244	.194
Moderate PA (mins/wk)	-.094	.525	-.301	.105
Vigorous PA (mins/wk)	-.403	**.005***	-.353	.056
MVPA (mins/wk)	-.166	.258	-.306	.100
Freedson MVPA†(mins/wk)	-.062	.675	-.263	.160

CG Control Group (n= 30) **HG** Haemophilia Group (n= 48) **mins/wk** Minutes per week **MVPA** Moderate Vigorous Physical Activity **PA** Physical Activity r_s Spearman's Rho; **† Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes; ***statistically significant at α= .05 (two-tailed).**

Participants from both groups were compared according to age categories (≥45 vs. <45 years). There were no significant differences between groups for duration of time spent in light PA [H(3)= 4.165; p= .244] or moderate PA [H(3)= 7.174; p= .067]. Statistically significant differences between groups were identified for vigorous PA [H(3)= 23.074; p= .000], MVPA [H(3)= 11.984; p= .007] and duration of MVPA spent in Freedson bouts [H(3)= 17.008; p= .001]. Post hoc analyses identified that adults ≥45 years in the HG were significantly less active in vigorous PA than adults <45 years in the HG (p= .046), adults ≥45 years in the CG (p= .030) and adults <45 years in the CG (p= .000). Adults <45 years in the HG were significantly less active in vigorous PA than adults <45 years in the CG (p= .003). There were no significant differences in vigorous PA between adults <45 years in the HG and adults ≥45 years in the CG (p= .542), or between adults <45 or ≥45 years in the CG (p= .073).

Adults ≥45 years in the HG were significantly less active in MVPA than adults <45 years in the CG (p= .001). There were no significant differences in MVPA between adults ≥45 years in the HG and adults <45 years in the HG (p= .342), or between adults ≥45 years in the HG and adults ≥45 years in the CG (p= .120). Adults <45 years in the HG were significantly less active in MVPA than adults <45 years in the CG (p= .013). There were no significant differences in MVPA between adults <45 years in the HG and adults ≥45 years in the CG (p= .413), or between adults <45 or ≥45 years in the CG (p= .222).

There was no significant difference in duration of MVPA spent in Freedson bouts between adults ≥45 years in the HG and adults <45 years in the HG (p= .852). Adults ≥45 years in the HG spent significantly less time in Freedson bouts compared to adults ≥45 years in the CG (p= .049), and adults <45 years in the CG (p= .000). Adults <45 years in the HG spent significantly less time in Freedson bouts compared to adults <45 years in the CG (p= .001). There were no significant differences in total Freedson bout duration between adults <45 years in the HG and adults ≥45 years in the CG (p= .066), or between adults ≥45 and <45 years in the CG (p= .319).

With regard to ActiGraph wear-time, there were no significant differences between the groups in the number of valid weekdays [H(3)= .487; p= .922] and valid weekend days [H(3)= 4.168; p= .244]. Duration of wear-time on valid days was significantly different between groups [H(3)= 17.977; p= .000]. Adults <45 years in the HG had significantly lower duration of wear-time than adults ≥45 years in the HG (p= .021), adults ≥45 years in the CG (p= .000), and adults <45 years in the CG (p= .001). Duration of wear-time between adults ≥45 years in the HG was not significantly different compared to adults ≥45 years in the CG (p= .091), or adults <45 years in the CG (p= .223). There was also no significant difference in the duration of wear-time between adults ≥45 and <45 years in the CG (p= .524).

3.3.3.4 Objective physical activity and bleeding phenotype

An examination of the relationship between ABR and objective PA parameters is presented in Table 3.5. ABR significantly predicted duration of time spent in MVPA [F(1,46)= 4.511; p=.039; R^2=.089; R^2_{adj}=.070; S_e=140.49], with ABR accounting for 8.9% of the explained variability in MVPA. The regression equation for this model was: Predicted MVPA= 190.365 + 13.371*(ABR) (Figure 3.2a). This model contained one outlier who spent 765 minutes per week in MVPA and residuals also appeared to be skewed, violating statistical assumptions (Appendix XVIX). The outlier was subsequently removed and both variables were transformed using square root transformations (sqrt) due to the presence of numerous "zero" values in the ABR dataset. These adjustments to the model appeared to resolve assumption violations (Appendix XX), although the regression model was no longer significant [F(1,45)= 1.127; p=.294; R^2=.024; R^2_{adj}=.003; S_e=4.64], with sqrt(ABR) representing 2.4% of the explained variability in sqrt(MVPA). The regression equation was: Predicted sqrt(MVPA)= 13.043 + (.732)*sqrt(ABR) (Figure 3.2b).

Table 3.5: Correlations between physical activity and bleeding phenotype

	Annualised Bleeding Rate	
	r_s	**p**
Light PA (mins/wk)	.055	.711
Moderate PA (mins/wk)	.154	.295
Vigorous PA (mins/wk)	.058	.697
MVPA (mins/wk)	.142	.334
Freedson MVPA†(mins/wk)	.156	.288

mins/wk Minutes per week **MVPA** Moderate-Vigorous Physical Activity **r_s** Spearman's Rho; **† Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes; **α= .05 (two-tailed).**

Figure 3.2a: Regression of Annualised Bleeding Rate (ABR) and Moderate-Vigorous Physical Activity (MVPA) (outlier included)

Regression equation: Predicted MVPA= 190.365 + 13.371*(ABR)

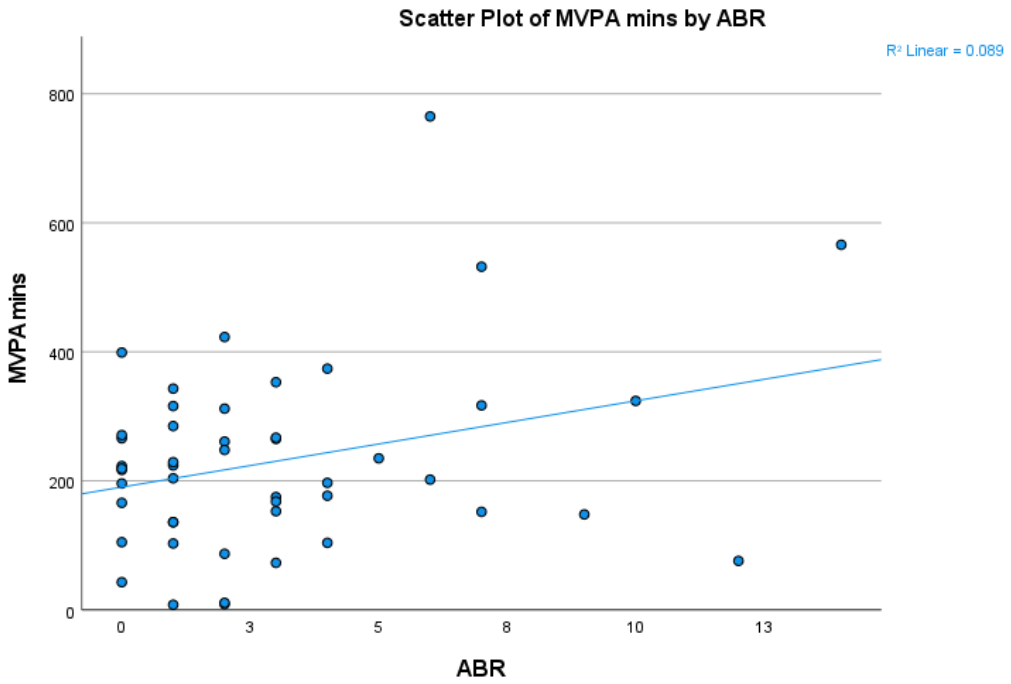
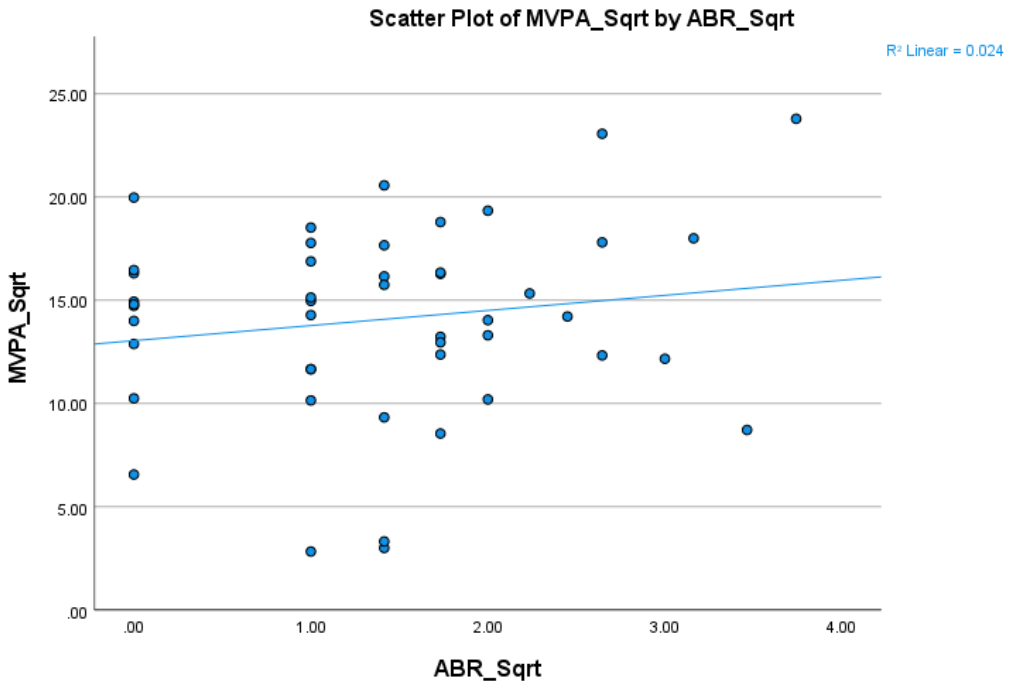


Figure 3.2b: Regression of Annualised Bleeding Rate (ABR) and Moderate-Vigorous Physical Activity (MVPA) (outlier removed, variables transformed)

Regression equation: Predicted sqrt(MVPA)= 13.043 + (.732)*sqrt(ABR)



3.3.3.5 Objective physical activity and joint health

An examination of the relationships between the HJHS, and the HJHS individual joint component scores, is presented in Table 3.6. The HJHS did not significantly predict duration of time spent in MVPA [$F(1,41)=.005$; $p=.942$; $R^2 = .000$; $R^2_{adj}=-.024$; $S_e=147.40$]. The HJHS accounted for none of the explained variability in MVPA. The regression equation was: Predicted MVPA= 233.874 + (-.127)*(HJHS) (Figure 3.3a). This model contained one outlier who spent 765 minutes per week in MVPA. This outlier appeared to cause some skewness in the residuals (Appendix XXI). When this outlier was removed the distribution of residuals improved, better meeting statistical assumptions (Appendix XXII). The model remained non-significant and the total HJHS did not significantly predict duration of time spent in MVPA [$F(1,40)=.047$; $p=.830$; $R^2 = .001$; $R^2_{adj}=-.024$; $S_e=125.77$]. The HJHS accounted for .1% of the explained variability in MVPA. The regression equation was: Predicted MVPA= 210.523 + .320*(HJHS) (Figure 3.3b).

Table 3.6: Correlations between physical activity and joint health

	Total HJHS		HJHS Ankle		HJHS Knee		HJHS Elbow	
	r_s	p	r_s	p	r_s	p	r_s	P
Light PA (mins/wk)	.015	.923	-.079	.614	.046	.770	-.003	.985
Moderate PA (mins/wk)	.031	.845	.107	.495	.112	.476	-.082	.602
Vigorous PA (mins/wk)	-.263	.088	.023	.886	-.271	.078	-.322	**.035***
MVPA (mins/wk)	-.005	.973	.080	.611	.086	.584	-.113	.470
Freedson MVPA†(mins/wk)	.062	.694	.124	.428	.073	.642	-.069	.662

HJHS Haemophilia Joint Health Score; **mins/wk** Minutes per week **MVPA** Moderate-Vigorous Physical Activity r_s Spearman's rho; **† Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes; ***statistically significant at α= .05 (two-tailed).**

Figure 3.3a: Regression of the Haemophilia Joint Health Score (HJHS) and Moderate-Vigorous Physical Activity (MVPA) (outlier included)

Regression equation: Predicted MVPA= 233.874 + (-.127)*(HJHS)

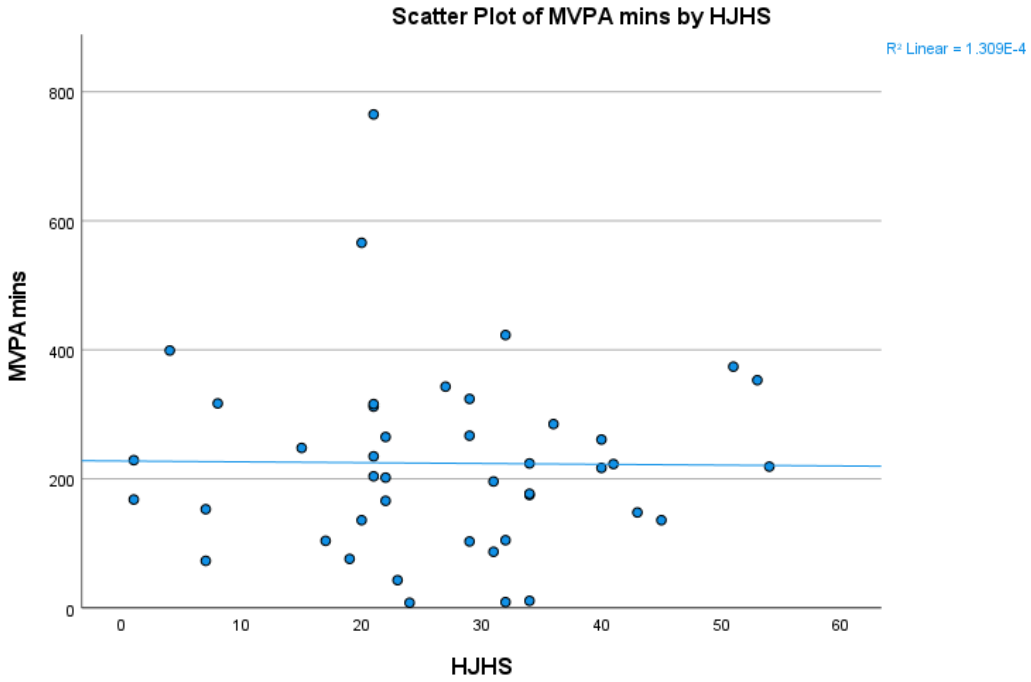
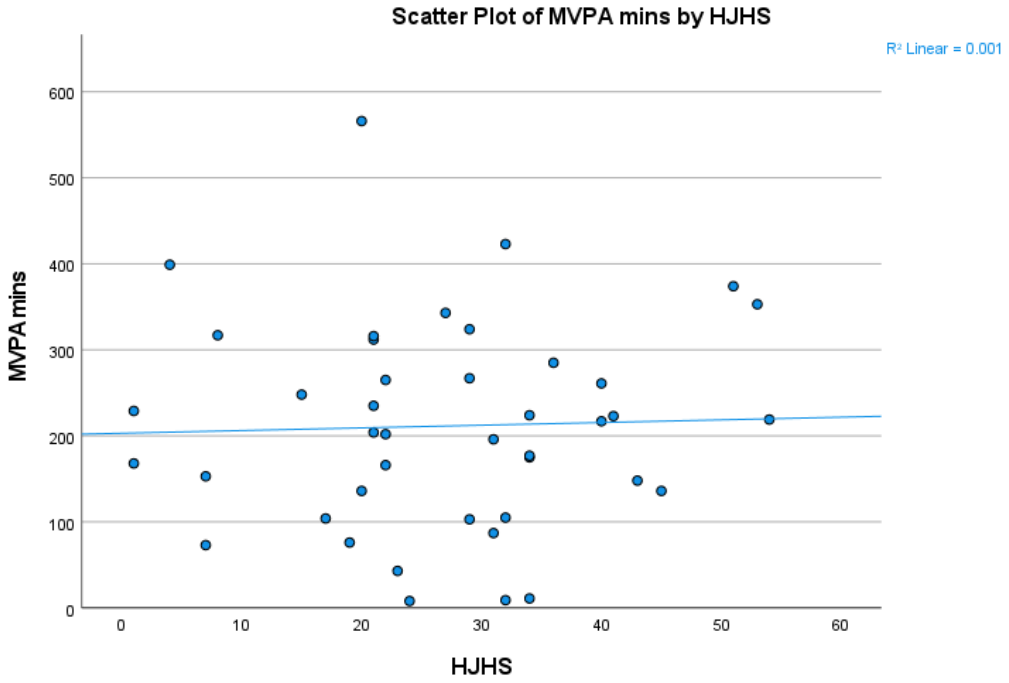


Figure 3.3b: Regression of Haemophilia Joint Health Score (HJHS) and Moderate-Vigorous Physical Activity (MVPA) (outlier removed)

Regression equation: Predicted MVPA= 210.523 + .320*(HJHS)



3.3.3.6 Objective physical activity and age prophylaxis commenced

An examination of the relationship between the age at which prophylaxis was commenced and objective PA parameters is presented in Table 3.7. The age at which prophylaxis was commenced did not significantly predict duration of time spent in MVPA [$F(1,35)=1.858$; $p=.182$; $R^2 = .050$; $R^2_{adj}=.023$; $S_e=143.94$]. It accounted for 5% of the explained variability in MVPA. The regression equation was: Predicted MVPA= 279.036 + (-1.688)*(age prophylaxis commenced) (Figure 3.4a). This model contained one outlier who spent 765 minutes per week in MVPA which appeared to cause some skewness in the residuals (Appendix XXIII). When this outlier was removed the distribution of residuals improved, better meeting the assumptions of regression (Appendix XXIV). The model remained non-significant and the age at which prophylaxis was commenced did not significantly predict duration of time spent in MVPA [$F(1,34)=1.046$; $p=.314$; $R^2 = .030$; $R^2_{adj}=.001$; $S_e=123.73$], accounting for 3% of the explained variability in MVPA. The regression equation was: Predicted MVPA= 251.276 + (-1.100)*(age prophylaxis commenced) (Figure 3.4b).

Table 3.7: Correlations between physical activity and age prophylaxis commenced

	Age at which prophylaxis was commenced	
	r_s	**p**
Light PA (mins/wk)	-.297	.074
Moderate PA (mins/wk)	-.168	.321
Vigorous PA (mins/wk)	-.407	**.012***
MVPA (mins/wk)	-.195	.248
Freedson MVPA†(mins/wk)	-.075	.661

mins/wk Minutes per week **MVPA** Moderate-Vigorous Physical Activity **r_s** Spearman's Rho; **† Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes; ***statistically significant at α= .05 (two-tailed).**

Figure 3.4a: Regression of age at which prophylaxis was commenced and Moderate-Vigorous Physical Activity (MVPA) (outlier included)

Regression equation: Predicted MVPA= 279.036 + (-1.688)*(age prophylaxis commenced)

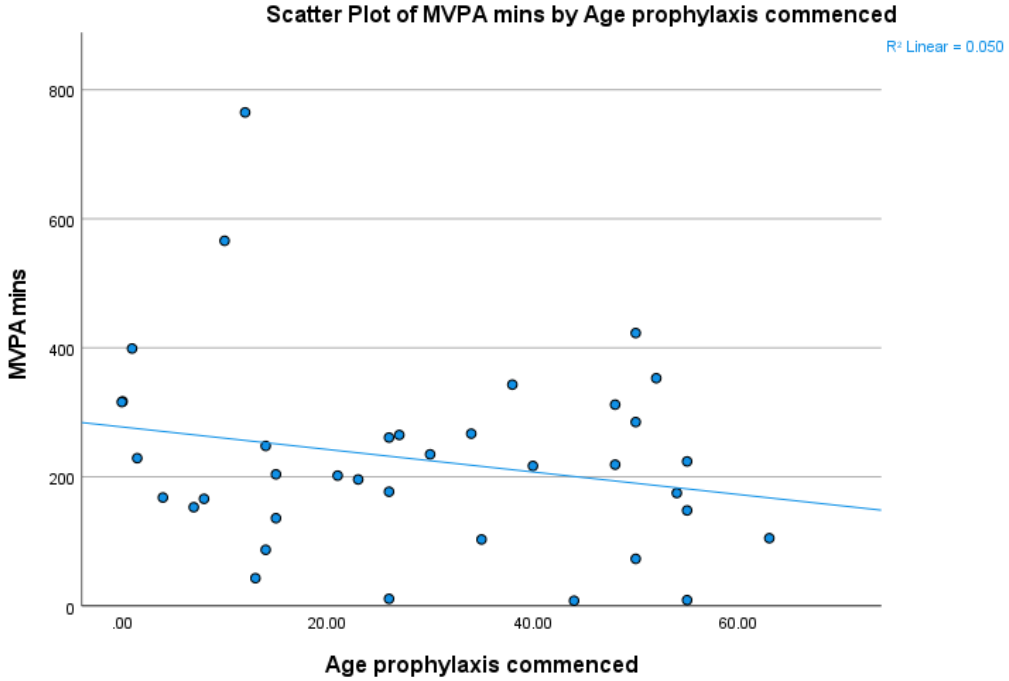
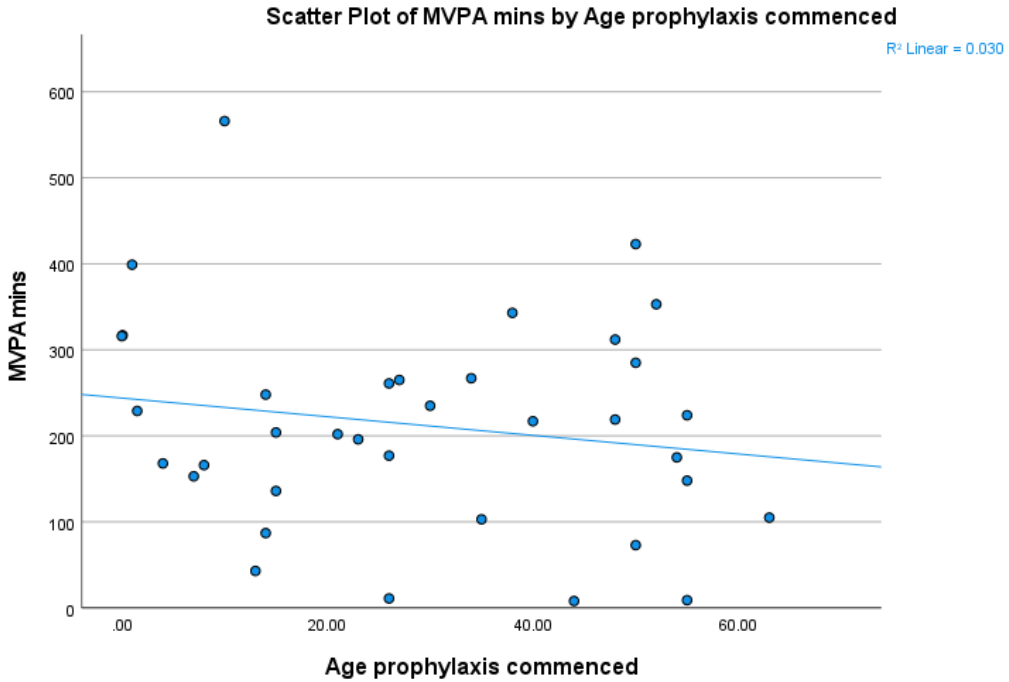


Figure 3.4b: Regression of age at which prophylaxis was commenced and Moderate-Vigorous Physical Activity (MVPA) (outlier removed)

Regression equation= Predicted MVPA= 251.276 + (-1.100)*(age prophylaxis commenced)



3.3.3.7 Objective physical activity, HCV and HIV

Objective PA, as well as age and clinical phenotypic parameters (which were considered potential confounders), were compared by categories of HCV history and HIV status, and results are presented in Table 3.8. Participants with a previous history of HCV were significantly older, had a significantly higher HJHS and commenced prophylaxis at a significantly older age than participants with no history of HCV. ABR was not significantly different between these groups. Participants with a history of HCV also spent significantly less time in vigorous PA compared to those with no history. There were no significant differences between groups in remaining PA parameters.

Participants who were HIV positive were also significantly older, had a significantly higher HJHS and commenced prophylaxis at a significantly older age than participants who were HIV negative. ABR was not significantly different between these groups. There were no significant differences between groups in PA parameters.

Table 3.8: Age, clinical phenotypic parameters and physical activity by HCV and HIV status

	HCV (previous history vs. no history)				HIV (positive vs. negative)			
	n	**Mean ranks**	**U**	**p**	**n**	**Mean ranks**	**U**	**p**
Age (years)	35 vs. 13	30.54 vs. 8.23	16.0	**.000***	36 vs. 12	34.46 vs. 21.18	335.5	**.004***
ABR (bleeds per year)	35 vs. 13	26.37 vs. 19.46	162.0	.124	36 vs. 12	23.21 vs. 24.93	200.5	.709
HJHS	32 vs. 11	25.14 vs. 12.86	75.5	**.004***	36 vs. 12	33.00 vs. 18.67	275.0	**.001***
Age prophylaxis commenced (years)	27 vs. 10	22.74 vs. 8.90	34.0	**.000***	29 vs. 8	17.09 vs. 25.94	171.5	**.039***
Light PA (mins/wk)	35 vs. 13	26.49 vs. 19.15	158.0	.107	36 vs. 12	25.58 vs. 24.14	229.0	.757
Moderate PA (mins/wk)	35 vs. 13	24.79 vs. 23.73	217.5	.817	36 vs. 12	20.79 vs. 25.74	171.5	.289
Vigorous PA (mins/wk)	35 vs. 13	22.23 vs. 30.62	307.0	**.037***	36 vs. 12	20.00 vs. 26.00	162.0	.145
MVPA (mins/wk)	35 vs. 13	24.13 vs. 25.50	240.5	.763	36 vs. 12	20.38 vs. 25.88	166.5	.239
Total Freedson MVPA†(mins/wk)	35 vs. 13	23.50 vs. 27.19	262.5	.416	36 vs. 12	20.63 vs. 25.79	169.5	.267

ABR Annualised Bleeding Rate **HCV** Hepatitis C Virus **HIV** Human Immunodeficiency Virus **HJHS** Haemophilia Joint Health Score **mins/wk** Minutes per week **MVPA** Moderate-Vigorous Physical Activity **PA** Physical Activity; **Groups compared using the Mann-Whitney U test; † Freedson=** Duration of time spent in bouts of MVPA ≥10 minutes**; *statistically significant at α= .05 (two-tailed)**.

3.4 Discussion

This study aimed to compare PA between adult PwMSH and adults without haemophilia, and additionally examine the relationship between PA and clinical phenotypic parameters. The majority of participants in both groups met PA guidelines; however, PwMSH spent significantly less time in moderate-vigorous intensity parameters of objectively measured PA compared to controls, which was also associated with age. Additionally, participation in various types of activity and sport were reported by PwMSH. Childhood participation in PA and sport was also significantly lower in PwMSH compared to controls. No significant relationships were found between PA and clinical phenotypic parameters including bleeding rate, joint health, the age at which prophylaxis was commenced.

3.4.1 Objectively measured physical activity

PwMSH were significantly less active in objectively measured MVPA parameters than adults without haemophilia in the present study. Similar findings have been reported by studies published in recent years that have used accelerometry to measure PA in adults with haemophilia (Timmer et al., 2018b, Putz et al., 2021). Despite these findings, 75% of PwMSH achieved PA guidelines of at least 150 minutes of moderate PA per week, which is notably higher than the male national average rate in Ireland (54%) (Healthy Ireland, 2019), however this interpretation may be affected by differences in methods used to assess PA. Carrasco et al. (2019) who also used an objective measure of PA, reported that 84.6% of adults with severe haemophilia achieved PA guidelines, which was similar but somewhat higher than findings of the present study. Furthermore, the rate of adults who achieved guidelines via sustained bouts of MVPA ≥10 minutes was significantly lower in PwMSH compared to controls. Notably, participants with haemophilia were significantly burdened by haemophilic arthropathy, therefore this finding may reflect the potential negative influence of pain and physical disability associated with chronic haemophilic arthropathy on exercise tolerance.

All participants included in this analysis met wear-time inclusion criteria of ≥10 hours per day on ≥4 days (including one weekend day). Although wear-time appeared to be similar between the HG and CG, statistical analysis revealed that differences in wear-time were significant, which implies that the CG wore the accelerometer for significantly longer on days that met minimum wear-time criteria. This may affect the interpretation of these results, however it is very difficult to control adherence to accelerometer wear-time in the field setting. Participants were told to wear the accelerometer during waking hours only, therefore variation in sleeping time, which was not measured in the present study, may alternatively explain differences in wear-time. Typically, the amount of time per day spent in moderate to vigorous intensities of PA is relatively brief compared to sedentary time and light intensity activity, therefore it is less likely that MVPA was substantially affected by a lower overall wear-time in the HG. Furthermore, wear-time appeared to be influenced by age, as further examination of PA by age group identified a significantly lower wear-time in younger PwMSH compared to older PwMSH and the CG.

3.4.2 Self-reported physical activity

Participation in a variety of types of activity and sport were reported by PwMSH who completed the Modifiable Activity Questionnaire. Interestingly, this also included a number of contact and collision sports such as hurling, soccer and boxing in some participants, which are generally discouraged in people with haemophilia. The World Federation of Hemophilia advises against participation in high contact, high velocity and collision sports, such as rugby, boxing and skiing, unless adequate prophylaxis has been taken to provide sufficient haemostatic coverage, and the potentially life-threatening risks have been considered (Srivastava et al., 2020). However, choices of activities or sports should also encompass individual interests, physical capabilities and available resources (Srivastava et al., 2020), thus the availability of prophylaxis and comprehensive care in Ireland appears to encourage PwMSH to engage in a wide variety of activities and sports. Similarities were found in the types of PA and sport undertaken by PwMSH and controls, which was also echoed in a study by (Versloot et al., 2019). However, the self-reported volume of PA undertaken differed across certain types of activity, which again, may reflect the physical burden of haemophilic arthropathy in PwMSH.

Participation in PA and sport during childhood was retrospectively assessed and appeared to be significantly lower in PwMSH compared to controls. Qualitative data provided insights on underlying reasons for childhood PA participation or non-participation. Themes identified as barriers to PA during childhood included fear of bleeds and joint injury, as well as a lack of permission to participate in PA and sport. Older adults in the present study did not have optimal access to prophylactic treatment regimens during childhood, which may have influenced attitudes and behaviours towards PA growing up. Equally, some participants reported that they went against advice that was given to them regarding PA and sports participation during childhood, which highlights how personality and intrapersonal factors may also influence PA behaviour. Fromme et al. (2007) have also reported that engagement in school sports during childhood was low in adults with haemophilia due to the perceived increased risk of bleeds and injuries. Longitudinal studies of PA and sports participation in younger cohorts with moderate and severe haemophilia would be interesting to ascertain the impact of primary prophylaxis treatment regimens and novel therapies on PA attitudes and participation across the life span. Barriers to PA in PwMSH of various ages evidently warrants further exploration.

3.4.3 Physical activity by type and severity of haemophilia

Objectively measured PA did not significantly differ between participants according to type and severity of haemophilia in this study. This is in keeping with findings from Timmer et al. (2020), who did not find differences in objectively measured PA according to haemophilia severity. Previous studies that compared self-reported PA between adults with different severities and types of haemophilia have reported conflicting findings. Interestingly, von Mackensen et al. (2016) reported adults with severe HA and HB who were treated with prophylaxis were significantly more active than adults with mild or moderate haemophilia ($p = .017$). No significant differences in PA measured by the International Physical Activity Questionnaire were identified between adults with mild, moderate

or severe haemophilia in a study by Goto et al. (2019). The same questionnaire was also assessed by Taylor et al. (2020), who reported adults with mild haemophilia were significantly more active in higher intensities of PA compared to adults with severe haemophilia, however no significant differences were found between severities for total PA volume. All participants with severe haemophilia and one participant with moderate HA who had a severe bleeding phenotype were treated with prophylaxis in the present study, whilst the remaining participants with moderate haemophilia were treated on demand. The haemostatic profile and bleeding phenotype of these groups, therefore, may have been similar overall. The recruitment of adults with mild haemophilia was not feasible for the present study, however future studies measuring PA should include them to determine if variation in PA is partially attributable to type and severity of haemophilia and their respective clinical phenotypes. It has also been proposed that people with HB present with a less severe bleeding phenotype than those with HA (Franchini and Mannucci, 2018), therefore studies with larger sample sizes of participants with HB may provide further insights on the relationship between haemophilia type and PA. The analysis of PA by haemophilia severity was ultimately limited by small and unequal sample sizes of subgroups in this study, therefore the potential risk of a type II statistical error must also be considered.

3.4.4 Physical activity and age

Higher levels of PA amongst younger people with haemophilia compared to older people with haemophilia have been reported in previous studies (Tiktinsky et al., 2009, Sherlock et al., 2010, Baumgardner et al., 2013, Niu et al., 2014, von Mackensen et al., 2016, Bouskill et al., 2016, Baumann et al., 2017, Versloot et al., 2019). Similarly, age appeared to influence certain parameters of PA in the present study, although light and moderate PA were not significantly impacted by age in either study group. Vigorous PA was significantly lower in older adults with haemophilia compared to younger adults with haemophilia, and compared to adults of any age in the CG. Furthermore, both older and younger adults with haemophilia spent a similar amount of time in MVPA compared to older adults in the CG, whilst younger adults with haemophilia were significantly less active in MVPA than younger adults in the CG. Time spent in Freedson bouts of MVPA was comparable between older and younger adults with haemophilia, although both age groups spent significantly less time in Freedson bouts compared to similarly aged controls. Overall findings therefore suggest that PwMSH, irrespective of age, appear to be less physically active in the duration of time they spend in MVPA compared to people without haemophilia of a similar age, and this may be more pronounced in younger adult PwMSH who appear to be comparably as active as older adults both with and without haemophilia. This may have potentially concerning implications for future chronic health risk, especially in the younger ageing population with haemophilia, therefore future longitudinal studies on PA and health are warranted. Examination of other cardiometabolic risk factors associated with physical inactivity, such as reduced cardiorespiratory fitness and obesity may also provide further insights on chronic health risk in ageing adults with haemophilia.

3.4.5 Physical activity and bleeding phenotype

No significant relationship was identified between objectively measured PA and ABR in the present study. Correlation and regression analyses between ABR and PA were weak, suggesting no definitive association between bleeds and habitual PA. Similar findings have been echoed in a number of previous studies that have examined the association between PA and bleeds (Ross et al., 2009, Khair et al., 2012, Broderick, 2013, von Mackensen et al., 2016, Goto et al., 2019, Versloot et al., 2019). Contrastingly, a potential association between bleeds and more strenuous intensities of PA have also been reported in other studies (Janco et al., 1996, Fromme et al., 2007, Tiktinsky et al., 2009, Sherlock et al., 2010, González et al., 2011, Broderick et al., 2012). The systematic review undertaken for this thesis presented in Chapter 1 concluded that the relationship between bleeds and PA was difficult to elucidate based off the available evidence to date. Certainly, the cross-sectional nature of the present study design limits the potential to establish causation or temporality between PA and bleeds. Furthermore, the majority of bleeds were not clinically verified. Participants with moderate haemophilia had a significantly higher number of clinically verified bleeds, which may reflect a higher inclination amongst people with severe haemophilia who are treated with prophylaxis to self-treat and manage perceived bleeding episodes at home. Bleeds may therefore have been under-reported as the ABR is limited by potential response and recall bias. Conversely, people with severe haemophilia with significant haemophilic arthropathy may perceive an exacerbation of arthropathy symptoms as a potential bleed, which may in turn lead to an overestimation of self-reported bleeds.

Modern day technology, with the use of smart phones, apps and fitness trackers, may facilitate the real-time measurement of bleeds, PA and treatment dosing in prospective, longitudinal studies. A recently published study by Konkle et al. (2021) prospectively measured bleeds, treatment regimen and PA using a commercial activity tracker and a real-time data collection app over six months in 54 adult PwMSH who were treated with prophylaxis. Activities with a high risk of collision were associated with an increased risk of bleeding. The risk of activity-related bleeding did not significantly increase with time between last prophylaxis infusion and activity, however prolonged time beyond 24 hours between the last infusion to commencing PA increased the risk of self-reported spontaneous bleeds. Participants in the study by Konkle et al. (2021) were treated with SHL products, which differs to participants in the present study who were predominantly treated with EHL products, however their study design may be used to inform the design of future studies examining the relationship between PA, bleeds and various treatment regimens.

3.4.6 Physical activity and joint health

Significant haemophilic arthropathy was evident in PwMSH in the present study, with the ankles being the most severely affected joints. Correlation and regression analyses revealed the HJHS was negligibly to weakly correlated with objectively measured PA, including both total and individual component joint scores. This is in contrast to findings reported by Putz et al. (2021), who found moderate, inverse correlations between the HJHS with VPA (r= -.56; p=.04; n= 13), and MVPA

sustained in bouts of ≥10 minutes (r=-.46; p=.110; n=13) measured using the ActiGraph, although findings are in agreement with weak correlations between objectively measured PA and the HJHS also reported by Carrasco et al. (2019). The HJHS was originally developed for children and younger PwH (Hilliard et al., 2006), and the HJHS has been validated and recommended for use in children and intensively treated young adults (Gouw et al., 2019). However, robust validation studies of the HJHS in older adults with more advanced haemophilic arthropathy are lacking (Gouw et al., 2019), and certain components of the score have been shown demonstrate significant floor and ceiling effects in adults (Kuijlaars et al., 2020). Its use is also limited in patients have undergone joint arthroplasty or arthrodesis. Evidently, the use of the HJHS to examine joint health in relation to PA in the present study, is limited, despite the lack of a feasible alternative measure of joint health available. Considering its widespread use in clinical practice, future studies should seek to validate or adjust the HJHS to be more sensitive to changes in joint health in adults with haemophilic arthropathy. Objective measures of joint health such as ultrasound scoring systems measured by trained professionals, have been recommended due to their ability to identify early, subclinical joint disease (Srivastava et al., 2020). Such measures may provide more a reliable measurement of joint health in future studies examining PA.

3.4.7 Physical activity and treatment regimen

The vast majority of adults with severe haemophilia, including one adult with moderate HA, were on tertiary prophylaxis in the present study, whilst only a small proportion were on primary or secondary prophylaxis from childhood. There was also significant heterogeneity in treatment products and the length of time participants were on various treatment products due to the mixed sample of participants with HA and HB. This, in conjunction with the small sample size, hindered the ability to compare PA and other clinical phenotypic parameters by treatment regimen. However, the age at which prophylaxis is commenced has been reported to be a strong predictor of long-term clinical outcomes in people with haemophilia (Srivastava et al., 2020), and has also been suggested to impact self-reported PA levels (Khawaji et al., 2011). Findings from the present study identified a moderate correlation between age at which prophylaxis was commenced and vigorous PA, yet correlation and regression analyses found a weak association between this measure and MVPA.

Interestingly, only a small proportion of participants took additional prophylaxis prior to engaging in PA in the present study, reflecting similar minorities who have tailored prophylaxis to sport and exercise in previous studies (Nazzaro et al., 2006, Köiter et al., 2009, Sherlock et al., 2010, Khair et al., 2012, von Mackensen et al., 2016, Goto et al., 2019). This may be due to relatively low participation in high intensity PA and sport in PwMSH. Alternatively, participants may have already tailored their exercise schedule to their prophylaxis regimen, resulting in a lack of need for any additional prophylaxis. The majority of participants were using EHL products in the present study, which could also explain why additional prophylaxis was not generally taken prior to exercise, as it has been reported that EHL products allow PwMSH to maintain or increase their PA levels whilst maintaining low bleeding rates in comparison to SHL products (Wang et al., 2016, Windyga et al.,

2016, Quon et al., 2017, Shrestha et al., 2021). Fear of bleeds and injuries may hinder PA participation in some PwMSH, therefore ensuring patients are educated on the benefits of timing treatment and exercise is important to optimise the potential for PA engagement. Additionally, novel therapies, including gene therapy and subcutaneously administered non-factor replacement products, have been developed in recent years, thus the impact of different treatments on the relationship between PA and bleed also warrants further investigation.

3.4.8 The impact of HCV and HIV on physical activity

The relationship between PA and comorbid HCV or HIV status has not been examined in previous studies of PA in people with haemophilia. A small number of studies and abstracts have highlighted the potential for adults with haemophilia who have a history of HCV and/ or HIV to report lower health-related quality of life compared to adults with no previous history (Fransen Van De Putte et al., 2011, Isfordink et al., 2021). All adults in the present study were previously treated and had successfully eradicated HCV, and a proportion with HIV were treating with antiretroviral therapy. Potential side effects of these treatments include fatigue and an increased bleeding tendency (Fransen van de Putte et al., 2013, Papadopoulos et al., 2018), which may further impact PA in affected patients. However, PA parameters were not significantly different according to HCV or HIV status, except for vigorous PA which was lower in adults with a previous history of HCV compared to participants with no history. Older age, later commencement of prophylaxis and a higher HJHS were also found in this group, therefore this interpretation may be confounded by these variables. This analysis was limited by the small sample size, but also by the lack of detailed information collected on treatment history of HCV and HIV. Further investigation of PA and quality of life in ageing adults with haemophilia who have comorbid HCV and HIV is warranted, in light of the additional comorbidities associated with these chronic conditions they may encounter.

3.4.9 Limitations

A number of limitations of this study have been discussed, however the following require further acknowledgement. The self-reported nature of a number of outcome measures, including the ABR, age at which prophylaxis was commenced and the Modifiable Activity Questionnaire, renders these measures prone to an increased risk of potential recall and response bias. Furthermore, this study took place during a treatment switchover period from a SHL product to an EHL product in participants with HA, therefore the ABR may not be fully representative of a stable ABR on EHL in the majority of participants with severe HA. The sample size recruited represented approximately ~15% of the target population of adult PwMSH in Ireland reported in 2017 (N= 330), and therefore may not be fully representative (WFH, 2017). Furthermore, the small sample recruited may have increased the risk of a type II error in statistical analyses. The CG especially may have been a more physically active and health conscious group, as they were predominantly recruited from a healthcare work setting. Participants were also aware they would receive feedback on their PA assessment, which may have introduced observation bias in this assessment. Accelerometry itself carries a risk of observation bias as research participants may change their PA behaviour due to an increased

awareness of being monitored, although it was emphasised to all participants to maintain typical levels of PA throughout the week of wearing the monitor. Furthermore, details of the advice patients receive in relation to PA engagement from their healthcare team were not collected in the present study, although anecdotally, PwMSH at the Irish treatment centre are generally advised to participate in PA and are encouraged to ensure they have sufficient factor coverage to enable them to exercise safely, as per best practice guidelines. They are also annually reviewed by the centre's clinical specialist physiotherapists who may also advise them regarding PA. Lastly, non-response bias could not be prevented, as characteristics of non-responders could not be ascertained due to ethical and confidentiality policies.

3.5 Conclusion

This study demonstrated that although the majority of PwMSH met PA guidelines, they were overall less physically active than adults without haemophilia in higher intensities of MVPA. This appeared to be more pronounced in younger adult PwMSH compared to controls of a similar age, although older adults were also less active in higher intensities of PA, as would be expected. Furthermore, childhood participation in PA was also significantly lower in PwMSH compared to controls, which may have influenced PA behaviour later in life, therefore further exploration of barriers to PA in PwMSH is needed. These findings collectively may have significant implications for the long-term health risk of the ageing haemophilia population, therefore other risk factors associated with physical inactivity and long-term health risk such as obesity, reduced physical fitness and cardiometabolic disorders (e.g. high blood pressure), warrant further investigation. Longitudinal studies of PA in people with haemophilia of various ages would provide further insights regarding the potential impact of primary prophylaxis from childhood, as well as novel treatments on PA and physical health. Lastly, no significant relationship was found between PA and clinical phenotypic parameters including bleeding phenotype, joint health and age at which prophylaxis was commenced. This warrants further exploration in future prospective, longitudinal studies involving a combination of validated, objective and subjective measurements of clinical phenotypic parameters and PA. Alternative barriers to PA also warrant further exploration.

Chapter 4: Study II: Physical fitness and cardiometabolic risk in adults with moderate and severe haemophilia

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4.1 Introduction

The life expectancy of the global haemophilia population increased between the 1970s-1990s, due to the introduction of replacement clotting factor concentrates and prophylactic treatment regimens (Mauser-Bunschoten et al., 2009, Boccalandro et al., 2018, Shapiro and Makris, 2019, Kempton et al., 2021). However, a number of incidents arose in the 1980s, where factor concentrates from unscreened donors were predominantly found to be positive for human immunodeficiency virus (HIV) and hepatitis C virus (HCV), amongst other blood-borne viruses. Unfortunately, this resulted in increased morbidity and mortality due to infections arising from viral exposure (including potential coinfection with both), thus tragically diminishing the previously increased life expectancy and improvements in quality of life of people with haemophilia (PwH) (Shapiro and Makris, 2019, Kempton et al., 2021, Alam et al., 2021). With the advent of viral inactivation of factor concentrates and novel treatments to supress HIV and eliminate HCV, the life expectancy of PwH has demonstrated a relative increase in recent years (Darby et al., 2007, Kempton et al., 2021). Consequently, cardiometabolic comorbidities associated both with general ageing and some older-generation antiviral regimens for HIV and HCV, including cardiovascular disease (CVD) and type 2 diabetes (TIIDM), are increasingly prevalent in the ageing haemophilia population (Mauser-Bunschoten et al., 2009, Shapiro and Makris, 2019, Kempton et al., 2021). Such comorbidities include hypertension (HTN), insulin resistance (IR), hyperlipidaemia (HLD), and obesity (Murray et al., 2020). Moreover, reduced cardiorespiratory fitness (CRF) is also a known risk factor for a variety of cardiometabolic diseases (Harber et al., 2017).

Considering elevated levels of circulating von Willebrand Factor and Factor VIII are associated with an increased risk of arterial thrombosis, it has been suggested that PwH (haemophilia A in particular) may theoretically be protected against cardiovascular thrombotic events due to the inherent deficiency of Factor VIII, and a perceived associated reduction in thrombin generation potential (Kamphuisen and ten Cate, 2014). However, the evidence to date reveals conflicting reports of cardiovascular and cardiometabolic morbidity and mortality in PwH compared to the general population, and some studies are also confounded by comorbid status of HIV or HCV, which may contribute to elevated cardiovascular risk and mortality (Darby et al., 2007, Miesbach et al., 2009, Tuinenburg et al., 2009, Biere-Rafi et al., 2010, Mostafa et al., 2010, Zwiers et al., 2012, Freiberg et al., 2013, Kamphuisen and ten Cate, 2014, Pocoski et al., 2014, Rizwan et al., 2015, Wang, 2016, Samuelson Bannow et al., 2019). Furthermore, the prevalence of HTN in PwH is reported to be higher than that of the general population, which is concerning as this may contribute to an increased

risk of intracranial haemorrhage in PwH (Street et al., 2006, Mauser-Bunschoten et al., 2009, Fransen van de Putte et al., 2012a, Samuelson Bannow et al., 2019).

An obesity pandemic is affecting the general global population and comorbidities associated with haemophilia may additionally contribute to a heightened risk of overweight and obesity, which is noted to be increasing in PwH at a similar rate (Wong et al., 2011). Increased Body Mass Index (BMI) has been associated with decreased joint range of movement in PwH, suggesting that overweight and obesity may negatively impact on haemophilic arthropathy (Soucie et al., 2004, Soucie et al., 2011). Furthermore, PwH with a history of HCV may be at an increased risk of adiposity post-treatment, as weight loss was a common side effect associated with older HCV treatments (Mauser-Bunschoten et al., 2009). Similarly, PwH who have HIV may be at an increased risk of central adiposity due to lipodystrophy (i.e. fat redistribution which may result in subcutaneous fat loss in the peripheries, and increased fat deposition in the abdomen), a potential side effect of antiviral therapy (Carr, 2003, Grinspoon and Carr, 2005, Nduka et al., 2016).

Features of physiological ageing including reductions in CRF, muscular strength, balance, flexibility, bone mineral density as well as increased adiposity and sarcopenia, are all associated with physical inactivity and an increased risk of falls and associated complications in the general population (Chodzko-Zajko et al., 2009). Grip strength and CRF have also been shown to moderate the association between PA and mortality (Celis-Morales et al., 2017). The impact of bleeds and chronic arthropathy may particularly accelerate these issues in ageing adult PwH (Stephensen and Rodriguez-Merchan, 2013). In addition to the potential for increased cardiometabolic risk with age, it would appear that adult people with moderate and severe haemophilia (PwMSH) may be at a significantly elevated overall health risk with age due to the lower levels of physical activity (PA) demonstrated amongst this cohort in Study I. The impact of clinical phenotypic parameters, as well as comorbid HCV and HIV status, on physical fitness and cardiometabolic risk is also not clear from the available evidence to date.

4.1.1 Aim

The primary aim of this study is to determine physical fitness and cardiometabolic risk in adult PwMSH. The secondary aim is to examine physical fitness and cardiometabolic risk parameters in relation to PA and clinical phenotype.

4.1.2 Objectives

4.1.2.1 Primary objectives

1) To compare BC between adult PwMSH and adults without haemophilia.

2) To compare physical fitness (CRF, grip strength and balance) between adult PwMSH and adults without haemophilia.

3) To compare vascular health between adult PwMSH and adults without haemophilia.

4) To compare the prevalence of cardiometabolic disorders (HTN, IR and HLD) between adult PwMSH and adults without haemophilia.

4.1.2.2 Secondary objectives

1) To determine the relationship between age and BC, physical fitness, vascular health and cardiometabolic disorder prevalence.

2) To determine the relationship between PA and BC, physical fitness, vascular health and cardiometabolic disorder prevalence.

3) To determine the relationship between clinical phenotypic parameters and BC, physical fitness, vascular health and cardiometabolic disorder prevalence in adult PwMSH.

4.2 Methodology

4.2.1 Study design and setting **(See sections 2.2-2.4)**

This cross-sectional study was conducted between April 2018 and March 2020. The haemophilia group (HG) were PwMSH recruited via convenience sampling from the national haemophilia database at the National Coagulation Centre, St. James's Hospital, Dublin. The control group (CG) were adults without haemophilia recruited from the staff and student populations of St. James's Hospital, Trinity College Dublin and Tallaght University Hospital. Research assessments took place at the Clinical Research Facility, St. James's Hospital. Ethical approval was obtained for this study (Appendix IV).

4.2.2 Participant recruitment **(See section 2.5)**

The clinical research team screened patients with haemophilia for study eligibility during routine outpatient clinics. Criteria included males aged ≥18 years with a clinical diagnosis of moderate (1-5%) or severe (<1%) Factor VIII or Factor IX deficiency, also known as Haemophilia A (HA) and Haemophilia B (HB), respectively. Individuals were not eligible if they had active inhibitors, a lack of capacity to provide informed consent, acute medical issues, non-resolved bleeds, or if they were non-ambulatory. Healthy male volunteers aged ≥18 years old without haemophilia or acute, unstable medical issues were recruited via an email and poster campaign to participate in the control arm of this study. Healthy volunteers were not eligible if they lacked capacity to provide informed consent or had any neuro- musculoskeletal disorder, HCV or HIV. Those eligible who expressed interest in the study were provided with the relevant Participant Information Leaflet (Appendix VIII). They were contacted one week later to determine study enrolment. Participants were scheduled for the research assessment at a time and date most convenient for them, and informed, written consent was obtained (Appendix IX).

4.2.3 Demographics and outcome measures

4.2.3.1 Demographic information

Age was recorded for both groups. Medical history was audited for the prevalence of HTN, IR and HLD (See section 2.6.5). Haemophilia type and severity, treatment regimen and product type, age at which prophylaxis was commenced (where applicable), inhibitor history, HCV and HIV status, and bone health history (where available), were also recorded in the HG.

4.2.3.2 Outcome measures

The following outcomes were assessed to fulfil the aims and objectives of this study:

- Bleeding phenotype was measured using the ***Annualised Bleeding Rate (ABR)*** (See section 2.6.2.1)
- Joint health was measured using the ***Haemophilia Joint Health Score (HJHS; version 2.1)*** (See section 2.6.2.2)
- Height was measured using the ***SECA 763 stadiometer*** (See section 2.6.5.1)
- Central adiposity was measured using the following anthropometric indices: Waist circumference (WC); hip circumference (HC); waist-hip ratio (WHR); waist-height ratio (WHtR) (See section 2.6.5.1)
- Weight, BMI, fat mass percentage (FM%) and skeletal muscle mass (SMM) were measured using the ***SECA mBCA 515 Multi-Frequency Body Composition Analyzer (Seca, Hamburg)*** (See section 2.6.5.1)
- Functional aerobic capacity was measured using the ***Six-Minute Walk Test (6MWT)*** (See section 2.6.4.1)
- Predicted maximal volume of oxygen consumption ($_{pred}VO_2max$) was measured using the ***YMCA Cycle Ergometer Test*** in the CG only (See section 2.6.4.1) A pilot study was originally planned for this thesis which aimed to obtain an objective measurement of CRF using the YMCA cycle ergometer test in PwMSH. This was ultimately not feasible to conduct within the remaining project timeframe after the Covid-19 pandemic restrictions were eased, however normative $_{pred}VO_2max$ data were successfully obtained in the CG before the pandemic. Therefore, simple linear regression was used to predict CRF in the HG using 6MWT scores based off a regression equation formed using normative $_{pred}VO_2max$ and 6MWT values.
- Grip strength was measured using the ***Jamar hand-grip dynamometer*** (See section 2.6.4.2)
- Balance was assessed using the ***One Leg Stand Test (OLST)*** **(**See section 2.6.4.3)
- Vascular health was assessed using resting blood pressure (BP) [systolic BP (SBP) and diastolic BP (DBP)] and arterial stiffness measured by the ***Mobil-O-Graph® PWA (IEM GmbH, Stolberg, Germany).*** Pulse wave velocity (PWV) is an indicator of aortic arterial

stiffness, whilst augmentation index (AIx) represents an estimate of combined aortic and peripheral arterial stiffness (See section 2.6.5.2)

- PA was objectively measured over one week using the ***ActiGraph GT3X-BT accelerometer (ActiGraph Corp, Pensacola, Florida, USA)*** (See section 2.6.3.1). Raw data were downloaded cleaned and analysed using the ActiLife software. PA was classified according to achievement of PA guidelines via the total amount of MVPA undertaken per week, as well as MVPA achieved via Freedson bouts (i.e. bouts of MVPA lasting ≥10 minutes) (Bull et al., 2020).

4.2.4 Statistical methods

Data were analysed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.). Normality of the data was assessed using a combination of the Shapiro-Wilk test and visual inspection of histograms, normal Q-Q plots and box and whisker plots. Continuous variables are described as mean ± standard deviation, as well as median and interquartile range (IQR: Q1, Q3). Data were skewed, therefore the Mann-Whitney U test was used to compare differences in continuous variables between two groups. In order to interpret the Mann-Whitney U test correctly, the shape of the data distribution in each group was inspected (Laerd, 2015a). A requirement of the Mann-Whitney U test is that the shape of the distribution of data in both groups of the independent variable must be inspected in order to determine how results of the test should be interpreted and reported (Laerd, 2015a). The shape of data distributions between groups differed, therefore mean ranks are reported, as recommended (Laerd, 2015a). The Kruskal-Wallis H test was used to compare continuous data between more than two groups. Dunn's post hoc pairwise comparisons were generated for the Kruskal-Wallis H test where results were statistically significant. Continuous variables in the HG were compared by groups of haemophilia type and severity, and moderate HA and HB were combined due to the small sample of these subgroups (i.e. severe HA vs. severe HB vs. moderate HA/HB). Continuous variables were also examined by age groups (≥45 vs. <45 years), achievement of PA guidelines (via total MVPA and MVPA achieved in Freedson bouts ≥10 minutes) (taken from findings in Chapter 3, section 3.3.3.1), HCV status (previous history and successfully treated vs. no history), HIV status (positive vs. negative) and coinfection status (Yes vs. No). Categorical data are described using frequencies and percentages. Chi-square tests of association were carried out between categorical variables. Fisher's exact test was run if expected cell counts were less than five. MVPA was compared according to balance status (impaired vs. normal), considering balance was a categorical variable.

The strength and direction of association between continuous variables were examined using Spearman's rank correlation analyses (r_s) due to the skewed distribution of the data. Strength of correlations were defined as follows: .00-.10 (Negligible); .10-.39 (Weak); .40-.69 (Moderate); .70-.89 (Strong); .90-1.00 (Very strong) (Schober et al., 2018). Simple linear regression was used to predict CRF in the HG using 6MWT scores based off a regression equation formed using normative $_{pred}VO_2max$ (dependent variable) and 6MWT (independent variable) values obtained from the CG.

The regression equation created used to estimate $_{pred}VO_2max$ from 6MWT scores in the HG was: $_{pred}VO_2max$= 15.628 + .032*(6MWT) [F(1, 28)= 2.754; p= .108; R^2= .090; R^2_{adj}= .057; S_E= 6.11]. Outliers were excluded to improve the fit of the linear regression equation. Missing data were excluded from analyses and are highlighted throughout the text, tables and figures as appropriate with accompanying explanations. Alpha (α)= .05 (two-tailed). Where p=.000, it is implied that p is <.0005 as per SPSS guidance (IBM, 2020b).

4.3 Results

4.3.1 Recruitment flow

Overall, 91 PwMSH were invited to participate, and 54 were enrolled (Appendix XVIII). One participant was excluded from this analysis as they did not complete the physical assessments. Furthermore, 62 adults without haemophilia expressed interest in participating, and 33 were enrolled. A final sample size of 86 participants were included in this analysis, which consisted of 53 participants in the HG, and 33 in the CG. Recruitment flow charts, including reasons for exclusion and non-participation, are provided in Figures 4.1a and 4.1b.

Figure 4.1a: Recruitment flow chart (haemophilia group)

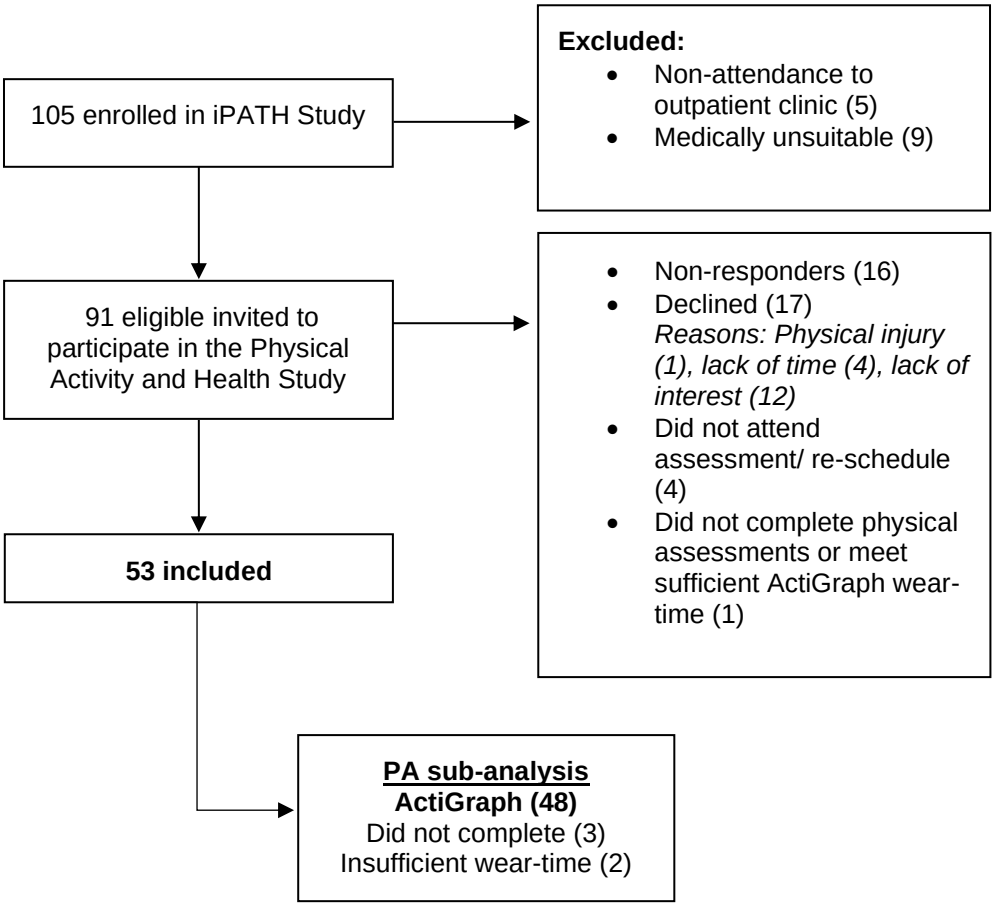
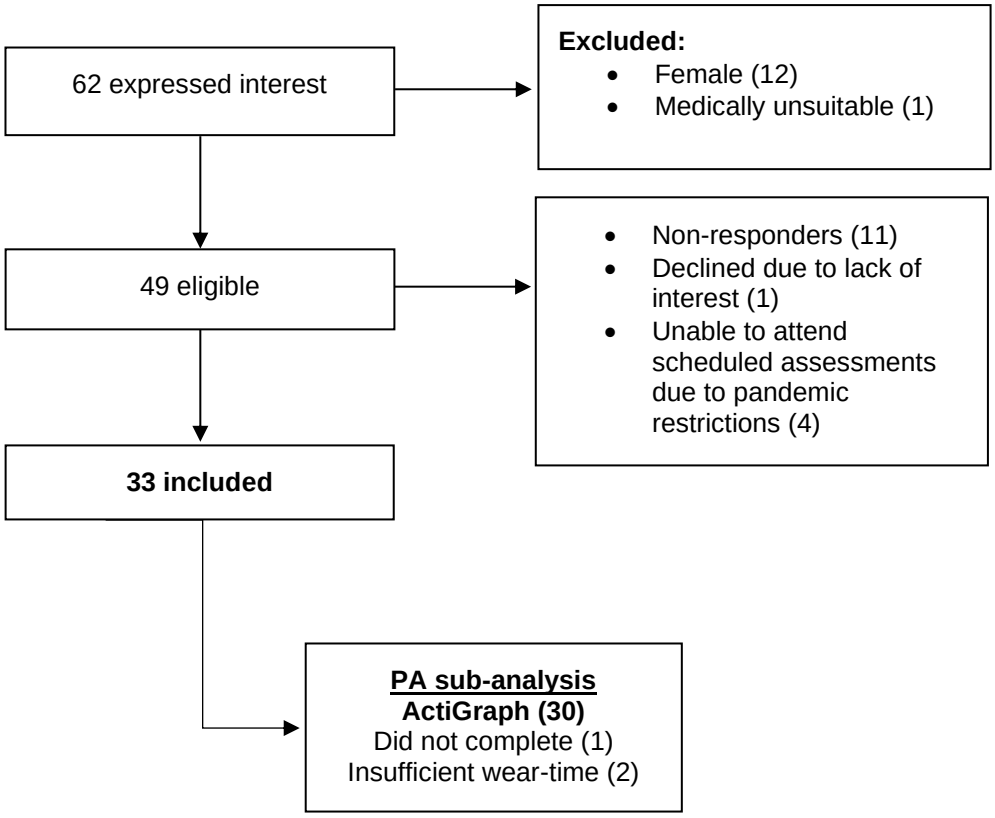


Figure 4.1b: Recruitment flow chart (control group)



4.3.2 Demographics and clinical phenotype

Demographics are presented in Tables 4.1a and 4.1b. Participants with severe haemophilia accounted for 86.8%, whilst 13.2% had moderate haemophilia. The mean age of the HG was 42 ± 13 [median: 44 IQR (33, 51)] years, and the mean age of the CG was 43 ± 9 [median: 43 IQR (36, 46)] years. There was no significant difference in age between the HG and CG [mean ranks: 42.62 vs. 44.91 (respectively); U= 828.0; p= .679]. There was also no significant difference in age by type and severity of haemophilia [H(2)= 4.125; p=.127]. All participants with severe haemophilia, and one participant with moderate HA, were treated with prophylaxis (88.7%). The remaining 11.3% had moderate haemophilia, and were treated on demand. A previous history of inhibitors was present in 11.3% of the total group. The median age at which participants commenced prophylaxis was 26 (12, 48) years. There was no significant difference between participants with HA or HB for the age at which prophylaxis was commenced [mean ranks: 18.91 vs. 25.50 (respectively); U= 240.5; p=.102]. At the time of the research assessment, extended half-life factor (EHL) products were used by 89.4% of participants on prophylaxis, whilst 6.4% used standard half-life factor (SHL) products, and 4.3% used a non-factor replacement product. Participants with HB were treated with EHL products for significantly longer prior to their research assessment compared to participants with HA [mean ranks: 34.53 vs. 17.23 (respectively); U= 398.0; p=.000]. Participants with HA were treated with a SHL product for significantly longer than participants with HB [mean ranks: 29.17 vs. 10.67 (respectively); U= 40.0; p=.000].

At least one bleeding event was reported by 79.2%, and there were no records of reported bleeding events in 20.8%. The median ABR was 2 (1, 4). No participant was diagnosed with a clinically defined target joint (i.e. ≥three spontaneous bleeds into one joint within six months). Causes of bleeds were ‘unknown’ and were not clinically verified or diagnosed in the majority of participants who reported a bleed. There were no significant differences between groups of haemophilia type and severity for ABR [H(2)= .752; p= .686], Annualised Joint Bleed Rate [H(2)= .639; p= .727], bleeds of unknown cause [H(2)= .802; p= .670], bleeds due to trauma [H(2)= 3.893; p= .143] or spontaneous bleeds [H(2)= 4.761; p= .092]. The number of clinically verified bleeds was significantly different between groups [H(2)= 12.316; p= .002]. There were no significant differences in the number of clinically verified bleeds between participants with severe HA and severe HB (p= .489), however participants with moderate HA/HB had a significantly higher number of clinically verified bleeds than participants with severe HA (p= .002), and severe HB (p= .001). The median HJHS was 29 (20, 34), indicating significant haemophilic arthropathy amongst the group. The ankles were the most severely affected joints, followed by the elbows and knees. There was no significant difference in the HJHS between participants with HA or HB [mean ranks: 24.06 vs. 25.47 (respectively); U= 262.0; p= .747]. With regard to medical history, 71.7% of participants had been treated successfully for HCV, 26.4% were HIV positive, 28.3% had undergone orthopaedic surgery and 42.1% had been formally diagnosed with osteopenia or osteoporosis.

4.3.3 Physical activity

Complete PA data were available for 48 participants in the HG and 30 participants in the CG. PA data were analysed, and results are reported in detail in Chapter 3 (see section 3.3.3.1), therefore only relevant results for this analysis are summarised. The median duration of time per week spent in MVPA was 218.0 (139.0, 305.3) minutes per week in the HG, and 318.5 (223.3, 461.3) minutes per week in the CG. The CG spent significantly more time per week in MVPA compared to the HG (p= .002). The median duration of time spent in MVPA classified as Freedson bouts (≥10 minutes) was 45.5 (11.0, 124.0) minutes per week in the HG, and 177.0 (82.5, 257.8) minutes per week in the CG. The CG spent significantly more time in MVPA classified as Freedson bouts compared to the HG (p= .000). PA guidelines were achieved by 72.9% of the HG and 90% of the CG (p= .088). Guidelines achieved via Freedson bouts were met by 18.8% in the HG, compared to 56.7% in the CG (p= .001).

Table 4.1a: Categorical demographic information by type and severity of haemophilia

	Total	Severe HA	Severe HB	Moderate HA	Moderate HB
	n (%)	n (%)	n (%)	n (%)	n (%)
n (%)	53 (100)	31 (58.5)	15 (28.3)	6 (11.3)	1 (1.9)
Inhibitor history					
History of inhibitors (non-active)	6 (11.3)	5 (83.3)	1 (16.7)	0	0
No history of inhibitors	47 (88.7)	26 (55.3)	14 (29.8)	6 (12.8)	1 (2.1)
Treatment regimen					
On demand	6 (11.3)	0	0	5 (83.3)	1 (16.7)
Prophylaxis	47 (88.7)	31 (66.0)	15 (31.9)	1 (2.1)	0
Treatment product					
Standard half-life product	3 (6.4)	3 (100)	0	-	-
Extended half-life product	42 (89.4)	26 (61.9)	15 (35.7)	1 (2.4)	-
Non-factor product	2 (4.2)	2 (100)	0	-	-
History of chronic infectious disease					
HCV (previous history, treated)	38 (71.7)	19 (50.0)	14 (36.8)	5 (13.2)	0
HCV (no previous history)	15 (28.3)	12 (80.0)	1 (6.6)	1 (6.6)	1 (6.6)
HIV (positive)	14 (26.4)	11 (78.6)	1 (7.1)	2 (14.3)	0
HIV (negative)	39 (73.6)	20 (51.3)	14 (35.9)	4 (10.3)	1 (2.5)
Orthopaedic surgical history					
Ankle arthrodesis	7 (13.2)	3 (42.9)	4 (57.1)	0	0
Total knee replacement	6 (11.3)	4 (66.7)	2 (33.3)	0	0
Total elbow replacement	1 (1.9)	1 (100)	0	0	0
Total hip replacement	1 (1.9)	0	1 (100)	0	0
Bone mineral density					
No report	15 (28.3)	7 (46.7)	4 (26.7)	3 (20.0)	1 (6.6)
Normal	22 (41.5)	17 (77.3)	4 (18.2)	1 (4.5)	0
Osteopenia	13 (24.5)	7 (53.8)	5 (38.5)	1 (7.7)	0
Osteoporosis	3 (5.7)	0	2 (66.7)	1 (33.3)	0

Values are presented as n (% of total); HA Haemophilia A **HB** Haemophilia B **HCV** Hepatitis C Virus **HIV** Human Immunodeficiency Virus

Table 4.1b: Continuous demographic information by type and severity of haemophilia

	Total (53)		Severe HA (31)		Severe HB (15)		Moderate HA (6)		Moderate HB (1)
	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Raw data
Age (years)	42 ± 13	44 (33, 51)	39 ± 12	38 (27, 49)	47 ± 13	47 (42, 55)	47 ± 13	50 (33, 59)	32
Age prophylaxis commenced (years)†	28 ± 19	26 (12, 48)	25 ± 19	23 (12, 40)	34 ± 18	38 (20, 51)	7 (raw data)		-
Joint Health‡									
HJHS Total	27 ± 13	29 (20, 34)	28 ± 12	29 (21, 38)	28 ± 14	27 (21, 34)	17 & 7 (raw data)		-
HJHS Elbow	8 ± 6	7 (2, 12)	9 ± 6	9 (4, 13)	6 ± 5	6 (1, 9)	1 & 0 (raw data)		-
HJHS Knee	5 ± 6	4 (1, 9)	5 ± 5	4 (0, 9)	6 ± 6	4 (2, 10)	5 & 1 (raw data)		-
HJHS Ankle	11 ± 5	12 (8, 15)	10 ± 6	11 (7, 14)	12 ± 5	12 (10, 15)	7 & 2 (raw data)		-
Global Gait Score	3 ± 1	4 (4, 4)	3 ± 1	4 (4, 4)	4 ± 1	4 (4, 4)	4 & 4 (raw data)		-
Bleeding phenotype									
ABR (Bleeds per year)	3 ± 3	2 (1, 4)	3 ± 3	2 (1, 4)	3 ± 4	2 (1, 4)	4 ± 3	4 (2, 7)	0
AJBR (Joint bleeds per year)	2 ± 2	1 (0, 3)	2 ± 2	1 (0, 3)	2 ± 2	1 (0, 3)	1 ± 2	1 (0, 3)	0
Spontaneous bleeds	0 ± 1	0 (0, 1)	0 ± 1	0 (0, 0)	0 ± 1	0 (0, 1)	1 ± 1	2 (0, 2)	0
Traumatic bleeds	1 ± 1	0 (0, 1)	0 ± 1	0 (0, 1)	1 ± 1	1 (0, 1)	1 ± 1	1 (0, 2)	0
Unknown cause bleeds	2 ± 3	1 (0, 3)	2 ± 3	1 (0, 3)	2 ± 3	0 (0, 3)	2 ± 3	1 (0, 4)	0
Clinically defined target joints	0 ± 0	0 (0, 0)	0 ± 0	0 (0, 0)	0 ± 0	0 (0, 0)	0 ± 0	0 (0, 0)	0
Clinically verified bleeds§	0 ± 1	0 (0, 0)]	0 ± 1	0 (0, 0)	0 ± 0	0 (0, 0)	2 ± 2	1 (1, 4)	0

	HA		HB	
Treatment product days¶	**Mean ± SD**	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**
Extended half-life factor days	179.5 ± 184.7	122 (28.0, 248.5)	436.0 ± 80.7	441 (364.0, 476.0)
Standard half-life factor days	217.5 ± 134.2	243 (116.5, 337.0)	3.5 ± 7.5	0 (0, 1)
Non-factor product days	371 & 491 (raw data)		-	

Values are presented as mean ± standard deviation and median (Q1, Q3); Raw values are presented where n= 1 or 2; ABR Annualised Bleeding Rate **AJBR** Annualised Joint Bleeding Rate **HA** Haemophilia A **HB** Haemophilia B **HJHS** Haemophilia Joint Health Score; **†** n= 41 (Severe HA= 27; Severe HB= 13; Moderate HA=1; Not applicable to 6 participants with moderate haemophilia; 6 participants with severe haemophilia did not answer question); **‡** n= 48 (not available for 5 participants with moderate haemophilia); **§** n= 42 who experienced bleeds**;** ¶ n= 47 on prophylaxis

4.3.4 Anthropometry and body composition

Descriptive statistics for anthropometric and BC variables of both groups are provided in Table 4.2a. Data are presented by type and severity of haemophilia in Table 4.2b.

4.3.4.1 Bioimpedance analysis

The prevalence of being overweight or obese was 66% in the HG, and 51.5% in the CG. BMI classification (i.e. normal vs. overweight/ obese; underweight excluded) was not significantly different between the HG and CG [$\chi 2(1) = 2.120$; p=.145; Fisher's Exact= .174; n= 85]. According to participants' age and gender specific FM% classification, 65.4% of the HG were classified as having poor FM% (see Chapter 2, Figure 2.7) compared to 45.5% in the CG [$\chi 2(1) = 3.284$; p=.070; Fisher's Exact= .077; n= 85]. There were no significant differences between the HG and CG, or within the HG for BMI, FM% or SMM.

4.3.4.2 Anthropometric indices involving waist circumference

The HG had a significantly higher prevalence of abdominal obesity than the CG according to WC [54.7% vs. 27.3%; $\chi 2(1) = 6.211$; p=.013; Fisher's Exact= .015], WHR [66.0% vs. 30.35%; $\chi 2(1) = 10.411$; p=.001; Fisher's Exact= .002] and WHtR [73.6% vs. 39.4%; $\chi 2(1) = 9.946$; p=.002; Fisher's Exact= .003]. There was no significant difference in HC between the HG and CG, however WC, WHR and WHtR were significantly higher in the HG compared to the CG. There were no significant differences between groups of haemophilia type and severity for WC, HC, WHR or WHtR.

Table 4.2a: Anthropometric and body composition parameters

		HG (53)		CG (33)				
		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ranks	U	p
Height (cm)		175.7 ± 7.2	174.4 (169.5, 181.8)	176.2 ± 6.7	176.1 (171.5, 180.9)	42.42 vs. 45.23	817.5	.613
Weight (kg)		83.9 ± 16.2	83.8 (72.0, 93.9)	81.8 ± 11.3	82.3 (73.7, 87.3)	44.95 vs. 41.17	951.5	.494
Body Mass Index (kg/m^2)		27.1 ± 4.6	27.0 (24.5, 30.3)	26.4 ± 3.9	25.2 (24.0, 28.6)	46.04 vs. 39.42	1009.0	.232
Fat Mass %†		27.5 ± 8.8	30.0 (22.3, 34.0)	24.5 ± 8.4	22.0 (18.5, 31.5)	46.85 vs. 36.94	1058.0	.071
Total Skeletal Muscle Mass (kg)†		30.4 ± 4.5	30.3 (27.2, 32.6)	30.9 ± 3.3	30.6 (28.5, 33.9)	41.33 vs. 45.64	771.0	.433
Skeletal Muscle Mass (kg)‡	**Left arm**	3.4 ± .6	3.4 (3.0, 3.6)	3.3 ± .4	3.3 (3.0, 3.7)	42.76 vs. 42.09	855.0	.902
	Right arm	3.5 ± .6	3.6 (3.1, 3.9)	3.5 ± .5	3.5 (3.2, 3.8)	42.74 vs. 42.14	853.5	.912
	Left leg	9.6 ± 1.5	9.4 (8.6, 10.5)	9.9 ± 1.0	9.6 (9.2, 10.7)	39.61 vs. 46.97	694.0	.177
	Right leg	9.7 ± 1.4	9.7 (8.7, 10.4)	10.0 ± 1.1	9.9 (9.5, 11.0)	39.11 vs. 47.74	668.5	.113
Waist Circumference (cm)		93.2 ± 11.2	94.4 (85.6, 102.0)	88.0 ± 13.0	85.5 (78.3, 94.5)	48.59 vs. 35.32	1144.5	**.016***
Hip Circumference (cm)		100.9 ± 8.5	100.0 (95.1, 106.1)	98.8 ± 5.4	98.7 (96.0, 100.6)	46.04 vs. 39.42	1009.0	.232
Waist-Hip Ratio		.92 ± .07	.94 (.87, .96)	.88 ± .09	.86 (.82, .93)	49.08 vs. 34.55	1170.0	**.009***
Waist-Height Ratio		.53 ± .07	.54 (.49, .57)	.50 ± .08	.48 (.45, .54)	48.47 vs. 35.52	1138.0	**.019***
		n (%)		n (%)				
Body Mass Index	**Underweight**	1 (1.9)		0		-	-	-
	Normal	17 (32.1)		16 (48.5)		-	-	-
	Overweight	22 (41.5)		12 (36.4)		-	-	-
	Obesity Class I	11 (20.7)		3 (9.1)		-	-	-
	Obesity Class II	2 (3.8)		2 (6.0)		-	-	-
Fat Mass %†	**Very lean**	1 (1.9)		2 (6.1)		-	-	-
	Excellent	3 (5.8)		3 (9.0)		-	-	-
	Good	5 (9.6)		6 (18.2)		-	-	-
	Fair	9 (17.3)		7 (21.2)		-	-	-
	Poor	2 (3.8)		2 (6.1)		-	-	-
	Very poor	32 (61.5)		13 (39.4)		-	-	-
Waist Circumference	**Normal**	24 (45.3)		24 (72.7)		-	-	-
	Increased	16 (30.2)		5 (15.2)		-	-	-
	Substantially increased	13 (24.5)		4 (12.1)		-	-	-
Waist-Hip Ratio	**Normal**	18 (34.0)		23 (69.7)		-	-	-
	Substantially increased	35 (66.0)		10 (30.3)		-	-	-
Waist-Height Ratio	**Normal**	14 (26.4)		20 (60.6)		-	-	-
	Increased	39 (73.6)		13 (39.4)		-	-	-

Continuous values are presented as mean ± standard deviation, and median (Q1, Q3); Categorical values are presented as n (% of total); CG Control Group; **HG** Haemophilia Group; **†** n= 52 as one participant unable to use bioimpedance analysis device; **‡** n= 51 as one participant unable to use bioimpedance analysis device and one participant's data was missing; **Values are compared using the Mann-Whitney U test; * statistically significant at α= .05 (two-tailed).**

Table 4.2b: Anthropometric and body composition parameters by type and severity of haemophilia

		Severe HA (31)		Severe HB (15)		Moderate HA (6)		Moderate HB (1)		
		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Raw data	H	p
Height (cm)		175.7 ± 7.0	**176.4 (169.6, 181.8)**	174.0 ± 5.0	**172.4 (169.3, 176.8)**	177.3 ± 11.1	**175.9 (167.2, 187.0)**	189.0	1.211	.546
Weight (kg)		83.4 ± 18.5	82.1 (70.0, 96.5)	83.0 ± 12.4	84.0 (75.9, 89.7)	85.4 ± 12.4	88.8 (71.9, 95.0)	103.0	1.065	.587
Body Mass Index (BMI; kg/m^2)		26.9 ± 5.0	26.8 (22.5; 29.9)	27.5 ± 3.9	28.3 (24.9, 30.6)	27.4 ± 5.5	25.8 (23.7; 33.8)	28.8	.565	.754
Fat Mass %† (FM%)		27.4 ± 8.7	28.5 (21.0, 36.0)	28.5 ± 9.0	32.0 (27.0, 34.0)	25.5 ± 10.9	23.0 (15.5, 36.8)	30	.745	.689
Total Skeletal Muscle Mass (SMM; kg)†		30.3 ± 4.9	30.5 (27.1, 32.8)	29.5 ± 3.1	29.5 (27.3, 31.0)	31.6 ± 5.2	30.7 (27.3, 35.1)	38.2	1.443	.486
SMM (kg)‡	**Left arm**	3.4 ± .6	3.4 (3.1, 3.7)	3.3 ± .5	3.4 (3.0, 3.5)	3.5 ± .8	3.3 (2.9, 4.0)	4.1	.637	.888
	Right arm	3.5 ± .7	3.6 (3.1, 3.9)	3.4 ± .5	3.6 (3.0, 3.6)	3.7 ± .8	3.4 (3.1, 4.4)	4.5	1.378	.711
	Left leg	9.6 ± 1.6	9.6 (8.5, 10.6)	9.2 ± .9	9.2 (8.5, 9.7)	10.0 ± 1.5	9.7 (8.7, 11.1)	12.2	4.491	.213
	Right leg	9.6 ± 1.5	9.7 (8.4, 10.7)	9.4 ± 1.0	9.4 (8.8, 10.0)	10.2 ± 1.5	9.9 (9.0, 11.4)	12.2	4.771	.189
Waist Circumference (WC; cm)		92.0 ± 12.0	93.6 (82.4, 101.5)	95.1 ± 9.4	96.1 (92.7, 100.5)	92.6 ± 12.3	93.3 (80.6, 105.4)	104.5	.866	.649
Hip Circumference (cm)		101.2 ± 9.6	99.8 (93.1, 106.7)	100.1 ± 6.3	100.0 **(97.7,103.8)**	100.3 ± 8.1	99.9 (92.3, 108.4)	108.3	.137	.934
Waist-Hip Ratio		.91 ± .10	.92 (.86, .96)	.95 ± .05	.95 (.93, 1.0)	.92 ± .10	.96 (.81, .98)	.96	3.689	.158
Waist-Height Ratio		.52 ± .07	.52 (.47, .57)	.55 ± .06	.55 (.54, .57)	.53 ± .10	.54 (.42, .62)	.55	1.801	.406
		n (%)		**n (%)**		**n (%)**		**n (%)**		
BMI category	**Underweight**	0		1 (6.7)		0		0	-	-
	Normal	12 (38.7)		3 (20.0)		2 (33.3)		0	-	-
	Overweight	12 (38.7)		7 (46.7)		2 (33.3)		1 (100)	-	-
	Obesity Class I	5 (16.1)		4 (26.6)		2 (33.3)		0	-	-
	Obesity Class II	2 (6.5)		0		0		0	-	-
FM% category†	**Very lean**	0		1 (6.7)		0		0	-	-
	Excellent	2 (6.7)		1 (6.7)		0		0	-	-
	Good	3 (10.0)		0		2 (33.3)		0	-	-
	Fair	6 (20.0)		1 (6.7)		2 (33.3)		0	-	-
	Poor	2 (6.7)		0		0		0	-	-
	Very poor	17 (56.6)		12 (80.0)		2 (33.3)		1 (100)	-	-
Waist Circumference	**Normal**	16 (51.6)		4 (26.7)		4 (66.7)		0	-	-
	Increased	8 (25.8)		8 (53.3)		0		0	-	-
	Substantially increased	7 (22.6)		3 (20.0)		2 (33.3)		1 (100)	-	-
Waist-Hip Ratio	**Normal**	13 (41.9)		3 (20.0)		2 (33.3)		0	-	-
	Substantially increased	18 (58.1)		12 (80.0)		4 (66.7)		1 (100)	-	-
Waist-Height Ratio	**Normal**	10 (32.3)		2 (13.3)		2 (33.3)		0	-	-
	Increased	21 (67.7)		13 (86.7)		4 (66.7)		1 (100)	-	-

Continuous values are presented as mean ± standard deviation and median (Q1, Q3); Categorical values are presented as n (% of total); HA Haemophilia A; **HB** Haemophilia B; **†** n= 30 for severe HA as one participant unable to use bioimpedance analysis device; **‡** n= 30 for severe HA as one participant unable to use bioimpedance analysis device and n= 14 for severe HB as one participant's data was missing; **Values are compared using the Kruskal-Wallis H test; * statistically significant at α= .05 (two-tailed).**

4.3.5 Physical fitness

Descriptive statistics for all physical fitness variables in the HG and CG are presented in Table 4.3a. Data are also presented by type and severity of haemophilia in Table 4.3b.

4.3.5.1 Functional aerobic capacity and cardiorespiratory fitness

The CG had a significantly higher 6MWT score compared to the HG. $_{pred}VO_2max$ measured using the YMCA cycle test in the CG was significantly higher than $_{pred}VO_2max$ estimated from 6MWT scores in the HG. There was no significant difference in 6MWT score by type and severity of haemophilia.

4.3.5.2 Maximal grip strength

In the HG, 90.7% of participants were right-handed, 7.0% were left-handed and 2.3% were ambidextrous. In the CG, 87.9% of participants were right-handed, 9.1% were left-handed and 3.0% were ambidextrous. Left grip strength was not significantly different between the HG and CG. Right grip strength was significantly lower in the HG compared to the CG. Grip strength was not significantly different between groups of haemophilia type and severity. When the marginal group (10.00-10.99% of a discrepancy) were excluded, a discrepancy >10% between right and left grip strength was not significantly different between the HG and CG [$\chi 2(1) = .777$; p=.378; Fisher's exact= .463; n= 71].

4.3.5.3 One leg stand test

Balance was impaired in 35.3% of the HG compared to 3.0% of the CG [$\chi 2(1) = 11.916$; p=.001; Fisher's exact= .000; n= 84]. Differences between the HG and CG were significant for left OLST performance [$\chi 2(1) = 7.277$; p=.007; Fisher's exact= .007; n= 84], and right OLST performance [$\chi 2(1) = 8.371$; p=.004; Fisher's exact= .003; n= 83]. Between group statistical analysis was not carried out by haemophilia type and severity due to the limited sample size, however balance was impaired in eight participants with severe HA, eight participants with severe HB and two participants with moderate HA.

Table 4.3a: Physical fitness parameters

N		HG (53) Mean ± SD	HG (53) Median (Q1, Q3)	CG (33) Mean ± SD	CG (33) Median (Q1, Q3)	Mean ranks	U	P
Six Minute Walk Test (m)†		557.2 ± 84.8	575.9 (509.2, 611.7)	663.7 ± 58.1	654.4 (625.0, 701.7)	29.61 vs. 60.08	205.5	**.000***
$_{pred}VO_2max$ (mL/kg/min)†		33.5 ± 2.7	34.1 (31.9, 35.2)	37.7 ± 7.7	36.4 (32.5, 42.4)	35.70 vs. 50.56	510.0	**.006***
Maximal grip strength (kg)‡	**Left hand**	39.9 ± 10.5	38.8 (33.8, 47.2)	42.9 ± 4.8	43.5 (39.9, 45.7)	35.52 vs. 44.92	563.5	.070
	Right hand	42.1 ± 10.4	40.2 (35.3, 47.2)	45.1 ± 7.9	45.7 (40.2, 50.7)	34.47 vs. 45.05	526.5	**.040***
		n (%)		**n (%)**				
>10% discrepancy in grip strength	**Yes (>10.99%)**	17 (38.6)		10 (30.3)		-	-	-
	No (<10.00%)	23 (52.3)		21 (63.6)		-	-	-
	Marginal (10.00-10.99%)	4 (9.1)		2 (6.1)		-	-	-
One leg stand test: Right leg¶	**≥ 30 seconds**	36 (72.0)		32 (97.0)		-	-	-
	< 30 seconds	14 (28.0)		1 (3.0)		-	-	-
One leg stand test: Left leg¶	**≥ 30 seconds**	38 (74.5)		32 (97.0)		-	-	-
	< 30 seconds	13 (25.5)		1 (3.0)		-	-	-

Continuous values are presented as mean ± standard deviation and median (Q1, Q3); Categorical values are presented as n (% of total); CG Control Group **HG** Haemophilia Group **$_{pred}VO_2max$** Predicted Maximal Volume of Oxygen Consumption**; †** HG (n= 50 as three participants unable to complete tests on the day); CG (n= 32 as one participant unable to complete test on the day); **‡** HG (Left hand n= 45 as dynamometer was sent away for servicing over period of testing for eight participants; Right hand n= 44 as additionally one participant was unable to perform test on right hand due to fear of pain provocation) **¶** HG (Left leg n= 51 as two participants were unable to complete the test due to severe arthropathy; Right leg n= 50 as additionally one participant was unable to complete test on right leg only); **Values are compared using the Mann-Whitney U test; * statistically significant at α= .05 (two-tailed).**

Table 4.3b: Physical fitness parameters by type and severity of haemophilia

		Severe HA (31)		Severe HB (15)		Moderate HA (6)		Moderate HB (1)		
		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Raw data	H	p
Six Minute Walk Test (m)†		550.4 ± 74.4	557.2 (506.3, 605.8)	561.4 ± 66.2	578.5 (529.5, 614.5)	554.4 ± 151.0	612.5 (401.8, 675.1)	714	2.332	.312
$_{pred}VO_2$max (mL/kg/min)†		33.2 ± 2.4	33.5 (31.8, 35.0)	33.6 ± 2.1	34.1 (32.6, 35.3)	33.4 ± 4.8	35.2 (28.5, 37.2)	38.5	-	-
Maximal grip strength (kg)‡	**Left hand**	39.9 ± 11.7	38.8 (30.8, 46.5)	39.8 ± 10.0	39.0 (32.5, 50.1)	40.4 ± 6.0	37.1 (35.6, 46.9)	41.4	.155	.925
	Right hand	42.4 ± 11.2	39.4 (34.4, 52.7)	41.0 ± 10.6	43.8 (37.7, 45.9)	41.6 ± 8.3	37.3 (35.3, 50.0)	45.9	.143	.931
		n (%)		**n (%)**		**n (%)**		**n (%)**		
>10% discrepancy in grip strength	**Yes (>10.99%)**	10 (58.8)		6 (35.3)		1 (5.9)		0	-	-
	No (<10.00%)	13 (56.5)		5 (21.7)		4 (17.4)		1 (4.3)	-	-
	Marginal (10.00-10.99%)	4 (100)		0		0		0	-	-
One leg stand test: Right¶	**≥ 30 seconds**	22 (61.1)		8 (22.2)		5 (13.9)		1 (2.8)	-	-
	< 30 seconds	6 (42.9)		7 (50.0)		1 (7.1)		0	-	-
One leg stand test: Left¶	**≥ 30 seconds**	22 (57.9)		10 (26.3)		5 (13.2)		1 (2.6)	-	-
	< 30 seconds	7 (53.8)		5 (38.5)		1 (7.7)		0	-	-

Continuous values are presented as mean ± standard deviation, and median (Q1, Q3); Categorical values are presented as n (% of total); HA Haemophilia A; **HB** Haemophilia B; **$_{pred}VO_2$max** Predicted Maximal Volume of Oxygen Consumption**; †** HG (Severe HA n= 29; Severe HB n= 14 as three participants unable to complete tests on the day); **‡** HG (Left hand: Severe HA n= 27; Severe HB n= 12; Moderate HA n= 5 as dynamometer was sent away for servicing over period of testing for eight participants; Right hand: Severe HB n= 11 as additionally one participant was unable to perform test on right hand due to fear of pain provocation) ¶ HG (Left leg: Severe HA n= 29 as two participants were unable to complete the test on the day; Right leg: Severe HA n= 28 as additionally one participant was unable to complete test on right leg only); **Values are compared using the Kruskal-Wallis H test; * statistically significant at α= .05 (two-tailed).**

4.3.6 Vascular health

Descriptive statistics for vascular health parameters are provided in Table 4.4a. Data are presented by type and severity of haemophilia in Table 4.4b.

4.3.6.1 Blood pressure

According to resting BP measurement, 39.6% of the HG were classified as hypertensive (grade I or grade II) compared to 42.4% in the CG. High-normal BP classification accounted for 34.0% in the HG, and 24.2% in the CG. There was no significant difference between the HG and CG in BP classification [$\chi 2(2) = 1.010$; $p = .604$]. Furthermore, there were no significant differences between the HG and CG, or within the HG for SBP or DBP.

4.3.6.2 Vascular stiffness

Vascular age was classified as normal or younger in in 64.7% of the HG, and 77.4% in the CG, whilst 35.3% of the HG and 22.6% of the CG had an older vascular age [$\chi 2(1) = 1.470$; $p = .225$; Fisher's Exact Test= .323; n= 82]. There was no significant difference between the HG and CG in aortic arterial stiffness measured by PWV, although AIx, which represents combined aortic and peripheral arterial stiffness, was significantly higher in the HG. There were no significant differences by groups of haemophilia type and severity for PWV or AIx.

4.3.7 Cardiometabolic disorders

In the HG, 13.2% had at least one cardiometabolic disorder, whilst 9.4% had more than one. In the CG, 9.1% had one cardiometabolic disorder, and no participant had more than one. HTN was formally diagnosed in 22.6% of the HG compared to 6.1% in the CG. IR was diagnosed in 5.7% of the HG (two participants had an elevated HbA1C and one had TIIDM). No participant in the CG had diagnosed IR. HLD was present in 7.5% of the HG compared to 3.0% in the CG. All participants were receiving appropriate medical treatment for their respective comorbidities.

Table 4.4a: Vascular health parameters

N		HG (53)		CG (33)		Mean ranks	U	p
		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)			
Systolic Blood Pressure (mmHg)		133.6 ± 13.1	134.0 (124.0, 137.5)	131.6 ± 10.3	133.0 (121.5, 139.0)	44.05 vs. 42.62	903.5	.797
Diastolic Blood Pressure (mmHg)		87.7 ± 13.1	83.0 (80.0, 92.0)	86.7 ± 9.2	85.0 (77.5, 95.0)	43.38 vs. 43.70	868.0	.954
Pulse Wave Velocity (m/s)†		6.9 ± 1.3	6.6 (5.8, 7.7)	6.9 ± 1.0	6.8 (6.2, 7.2)	41.03 vs. 42.27	766.5	.818
Augmentation Index (%)†		11.0 ± 10.4	8.0 (3.0, 18.0)	5.3 ± 9.7	3.0 (-3.0, 13.0)	46.52 vs. 33.24	1046.5	**.014***
		n (%)		n (%)				
Blood Pressure	**Normal**	14 (26.4)		11 (33.3)		-	-	-
	High-normal	18 (34.0)		8 (24.2)		-	-	-
	Grade 1 HTN	15 (28.3)		11 (33.3)		-	-	-
	Grade 2 HTN	6 (11.3)		3 (9.1)		-	-	-
Vascular age†	**Younger**	6 (11.8)		4 (12.9)		-	-	-
	Normal	27 (52.9)		20 (64.5)		-	-	-
	Older	18 (35.3)		7 (22.6)		-	-	-

Continuous values are presented as mean ± standard deviation, and median (Q1, Q3); Categorical values are presented as n (% of total); CG Control Group **HG** Haemophilia Group **HTN** Hypertension; **†** HG n= 51 and CG n= 31 due to absence of equipment; **Values are compared using the Mann-Whitney U test; * statistically significant at α= .05 (two-tailed).**

Table 4.4b: Vascular health parameters by type and severity of haemophilia

		Severe HA (31)		Severe HB (15)		Moderate HA (6)		Moderate HB (1)		
		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Raw data	H	p
Systolic Blood Pressure (mmHg)		133.7 ± 12.9	134.0 **(125.0,138.0)**	133.1 ± 14.9	131.0 **(123.0,135.0)**	134.8 ± 12.7	132.5 **(123.5,145.5)**	130	.255	.880
Diastolic Blood Pressure (mmHg)		87.6 ± 13.7	83.0 (80.0, 92.0)	88.6 ± 13.5	86.0 (81.0, 92.0)	86.5 ± 12.5	81.0 (78.5, 95.8)	86	.385	.825
Pulse Wave Velocity (m/s)†		6.6 ± 1.3	6.2 (5.5, 7.5)	7.3 ± 1.2	7.3 (6.5, 8.2)	7.3 ± 1.2	7.7 (5.9, 8.3)	5.9	4.507	.105
Augmentation Index (%)†		11.8 ± 8.9	9.0 (5.0, 16.5)	9.4 ± 11.7	8.0 (.0, 19.0)	9.0 ± 14.7	2.5 (-1.5, 22.3)	21	1.284	.526
		n (%)		n (%)		n (%)		n (%)		
Blood Pressure	**Normal**	7 (22.5)		5 (33.3)		2 (33.3)		0	-	-
	High-normal	11 (35.5)		5 (33.3)		1 (16.7)		1	-	-
	Grade 1 HTN	10 (32.3)		3 (20.0)		2 (33.3)		0	-	-
	Grade 2 HTN	3 (9.7)		2 (13.3)		1 (16.7)		0	-	-
Vascular age†	**Younger**	2 (6.9)		3 (20.0)		1 (16.7)		0	-	-
	Normal	16 (55.2)		7 (46.7)		3 (50.0)		1	-	-
	Older	11 (37.9)		5 (33.3)		2 (33.3)		0	-	-

Continuous values are presented as mean ± standard deviation, and median (Q1, Q3); Categorical values are presented as n (% of total); CG Control Group **HG** Haemophilia Group **HTN** Hypertension; **†** Severe HA n= 29 due to absence of equipment; **Values are compared using the Kruskal-Wallis H test; * statistically significant at α= .05 (two-tailed).**

4.3.8 Age, physical fitness and cardiometabolic risk

Age was examined in relation to physical fitness and cardiometabolic risk parameters in both groups using Spearman's rank order correlation analyses, and findings are presented in Table 4.5a. Age was weakly correlated with BMI in both groups. FM%, SMM and WC were weakly correlated with age in the HG, but moderately correlated with age in the CG. Age was moderately correlated with WHR and WHtR in both groups. Weak, inverse correlations were demonstrated between age and all physical fitness parameters in both groups. Correlations between age and BP were weak in both groups. PWV was very strongly correlated with age in both groups (Figure 4.2a and 4.2b). A weak, inverse correlation was found between age and AIx in the HG (Figure 4.3a), whilst a moderate, positive correlation was demonstrated between these variables in the CG (Figure 4.3b).

Physical fitness and cardiometabolic risk parameters in both groups were compared by age (≥45 vs. <45 years) using the Mann-Whitney U test, and findings are presented in Table 4.5b. There was no significant difference in BMI according to age category in either the HG or CG. FM% was significantly higher in adults ≥45 years in both groups. SMM was lower in adults ≥45 years in both groups, which was significant in the HG but not the CG. WC, WHR and WHtR were all significantly higher in adults ≥45 years in both groups. There were no significant differences in physical fitness parameters by age, however participants who had a >10% discrepancy between left and right grip strength were significantly older in the HG [mean ranks: 25.29 vs. 16.96 (respectively); U= 277.0; p= .025], but not in the CG [mean ranks: 16.85 vs. 15.60 (respectively); U= 113.5; p= .724]. Participants with impaired balance were significantly older than those who had normal balance in the HG [mean ranks: 34.75 vs. 21.23 (respectively); U= 139.5; p= .002]. Only one participant in the CG had impaired balance, and they were ≥45 years old. BP was not significantly different by age in either group, however PWV was significantly higher in older adults in both groups. AIx was significantly higher in older adults in the CG. Differences between AIx were not significant in the HG.

Age was significantly older in participants with formally diagnosed HTN in the HG compared to those without HTN [n= 12 vs. 41; mean ranks: 41.50 vs. 22.76 (respectively); U= 420.0; p= .000]. Both participants with HTN in the CG were ≥45 years. Two participants in the HG with IR were ≥45 years, whilst the remaining one was <45 years. All participants with HLD from both groups were ≥45 years. Statistical comparisons were not carried out on these groups due to the limited sample size.

Table 4.5a: Spearman rank order correlation analyses between age with physical fitness and cardiometabolic risk parameters

	Age (HG)			Age (CG)		
	n	r_s	P	n	r_s	p
Body Mass Index (kg/m^2)	53	.206	.138	33	.251	.159
Fat Mass %	52	.379	**.006***	33	.628	**.000***
Skeletal Muscle Mass (kg)	52	-.390	**.004***	33	-.555	**.001***
Waist Circumference (cm)	53	.397	**.003***	33	.406	**.019***
Hip Circumference (cm)	53	.080	.571	33	.074	.681
Waist-Hip Ratio	53	.671	**.000***	33	.491	**.004***
Waist-Height Ratio	53	.548	**.000***	33	.458	**.007***
Six Minute Walk Test (m)	50	-.188	.190	32	-.368	**.038***
$_{pred}VO_2max$ (mL/kg/min)	50	-.188	.190	32	-.372	**.036***
Left grip strength (kg)	45	-.391	**.008***	33	-.227	.203
Right grip strength (kg)	44	-.396	**.008***	33	-.317	.072
Systolic BP (mmHg)	53	.069	.623	33	.008	.964
Diastolic BP (mmHg)	53	.277	**.045***	33	.388	**.026***
Pulse Wave Velocity (m/s)	51	.921	**.000***	31	.906	**.000***
Augmentation Index (%)	51	-.241	.089	31	.513	**.003***

BP Blood Pressure **CG** Control Group **HG** Haemophilia Group **$_{pred}VO_2max$** Predicted Maximal Volume of Oxygen Consumption **r_s** Spearman's Rho; *** statistically significant at α= .05 (two-tailed).**

Table 4.5b: Mann-Whitney U test results of physical fitness and cardiometabolic risk parameters compared by age

	HG (≥45 vs. <45 years)				CG (≥45 vs. <45 years)			
	n	**Mean ranks**	**U**	**P**	**n**	**Mean ranks**	**U**	**p**
Body Mass Index (kg/m^2)	24 vs. 29	30.10 vs. 24.43	273.5	.183	11 vs. 22	20.50 vs. 15.25	82.5	.143
Fat Mass %	23 vs. 29	32.83 vs. 21.48	188.0	**.007***	11 vs. 22	24.59 vs. 13.20	37.5	**.001***
Skeletal Muscle Mass (kg)	23 vs. 29	20.96 vs. 30.90	461.0	**.019***	11 vs. 22	12.36 vs. 19.32	172.0	.053
Waist Circumference (cm)	24 vs.29	33.85 vs. 21.33	183.5	**.003***	11 vs. 22	22.91 vs. 14.05	56.0	**.012***
Hip Circumference (cm)	24 vs.29	28.42 vs. 25.83	314.0	.543	11 vs. 22	19.00 vs. 16.00	99.0	.418
Waist-Hip Ratio	24 vs.29	38.27 vs. 17.67	77.5	**.000***	11 vs. 22	23.64 vs. 13.68	48.0	**.004***
Waist-Height Ratio	24 vs. 29	36.19 vs. 19.40	127.5	**.000***	11 vs. 22	23.41 vs. 13.80	50.5	**.006***
Six Minute Walk Test (m)	24 vs. 26	22.54 vs. 28.23	383.0	.168	11 vs. 21	13.68 vs. 17.98	146.5	.223
$_{pred}VO_2max$ (mL/kg/min)	24 vs. 26	22.54 vs. 28.23	383.0	.168	11 vs. 21	12.73 vs. 18.48	157.0	.104
Left grip strength (kg)	21 vs. 24	19.36 vs. 26.19	328.5	.082	11 vs. 22	14.05 vs. 18.48	153.5	.218
Right grip strength (kg)	20 vs. 24	18.85 vs. 25.54	313.0	.085	11 vs. 22	12.59 vs. 19.20	169.5	.063
Systolic BP (mmHg)	24 vs. 29	28.06 vs. 26.12	322.5	.648	11 vs. 22	15.95 vs. 17.52	132.5	.665
Diastolic BP (mmHg)	24 vs. 29	31.17 vs. 23.55	248.0	.074	11 vs. 22	20.23 vs. 15.39	85.5	.178
Pulse Wave Velocity (m/s)	22 vs. 29	38.84 vs. 16.26	36.5	**.000***	11 vs. 20	24.59 vs. 11.28	15.5	**.000***
Augmentation Index (%)	22 vs. 29	21.73 vs. 29.24	413.0	.073	11 vs. 20	22.82 vs. 12.25	35.0	**.001***

BP Blood Pressure **CG** Control Group **HG** Haemophilia Group **$_{pred}VO_2max$** Predicted Maximal Volume of Oxygen Consumption; *** statistically significant at α= .05 (two-tailed).**

Figure 4.2a: Scatterplot of age and pulse wave velocity in participants with haemophilia

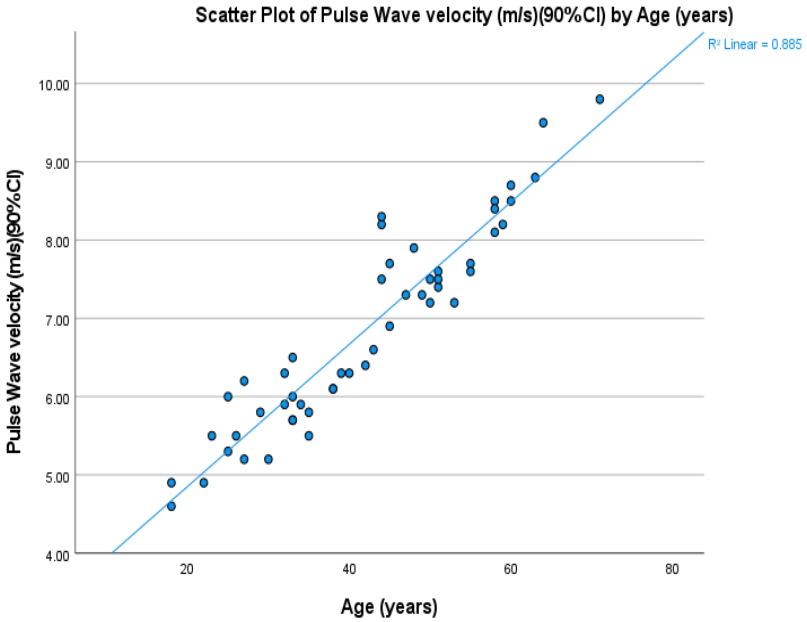


Figure 4.2b: Scatterplot of age and pulse wave velocity in participants without haemophilia

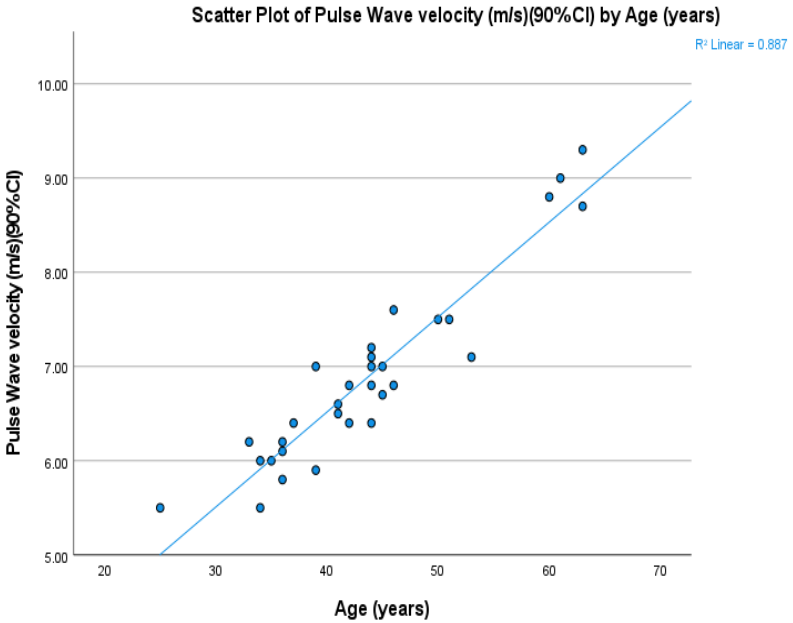


Figure 4.3a: Scatterplot of age and augmentation index in participants with haemophilia

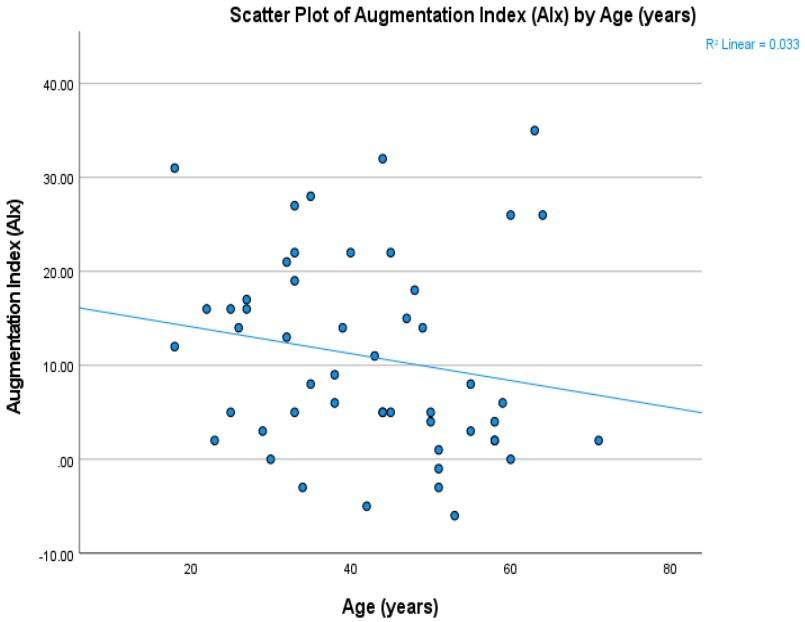
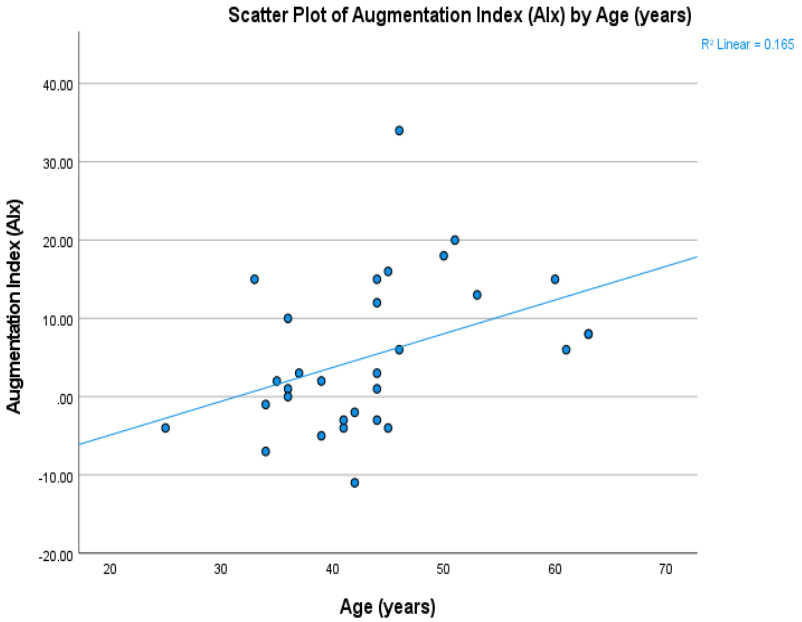


Figure 4.3b: Scatterplot of age and augmentation index in participants without haemophilia



4.3.9 Physical activity, physical fitness and cardiometabolic risk parameters

Durations of time spent per week in total MVPA and MVPA carried out in Freedson bouts (≥10 minutes) were examined in relation to fitness and cardiometabolic risk parameters in both groups using Spearman's rank order correlation analyses, and findings are presented in Table 4.6a. All variables were weakly correlated with MVPA parameters in the HG. Moderate, inverse correlations were found between MVPA parameters and BMI, FM%, WC and WHtR in the CG. The 6MWT was also moderately correlated with total MVPA in the CG, whilst MVPA achieved in Freedson bouts was moderately, inversely correlated with left grip strength.

Physical fitness and cardiometabolic risk parameters were compared according to achievement of PA guidelines (Bull et al., 2020) in both groups, and findings are presented in Table 4.6b. FM%, WC, WHR and WHtR were significantly lower in participants who achieved PA guidelines via total MVPA in the CG, but differences between groups were not significant for these parameters in the HG. SMM was significantly higher in participants who achieved PA guidelines via total MVPA in the HG, but this was not significant in the CG. There were no significant differences between categories for the remaining parameters in either study group. BMI and WHtR were significantly lower in participants who achieved PA guidelines via MVPA classified as Freedson bouts in the CG, but this was not significantly different in the HG. Left grip strength was significantly lower in participants who achieved PA guidelines via MVPA classified as Freedson bouts in both groups. There were no significant differences between categories for the remaining parameters in either study group. MVPA parameters were not significantly different between participants with impaired balance compared to those with normal balance in the HG [Total MVPA: mean ranks: 24.50 vs. 23.69 (respectively); U= 252.0; p= .844; Freedson MVPA: mean ranks: 21.78 vs. 25.38 (respectively); U= 301.0; p= .381]. The one participant with impaired balance in the CG did not achieve either set of PA guidelines.

In participants without HTN in the HG (n= 37), 75.7% and 21.6% met PA guidelines via total MVPA and MVPA achieved via Freedson bouts (respectively). In participants who had formally diagnosed HTN in the HG (n= 11), 63.6% and 9.1% met PA guidelines via total MVPA and MVPA achieved via Freedson bouts (respectively). In the CG, the two participants with HTN both met PA guidelines via total MVPA but not via Freedson bouts. There were no significant differences in total or Freedson MVPA between participants with and without HTN in the HG [Total MVPA: n= 12 vs. 38; mean ranks: 24.08 vs. 25.95 (respectively); U= 211.0; p= .699; Freedson MVPA: n= 12 vs.38; mean ranks: 21.38 vs. 26.80 (respectively); U= 178.5; p= .260]. Two of three participants with IR in the HG met PA guidelines via total MVPA but not via Freedson bouts. The remaining participant did not meet either set of guidelines. Two of four participants with HLD in the HG met PA guidelines via total MVPA but not via Freedson bouts, one participant met both sets of guidelines, and the remaining participant did not meet either. The one participant with HLD from the CG met PA guidelines via total MVPA and MVPA classified as Freedson bouts.

Table 4.6a: Spearman rank order correlation analyses between physical activity with fitness and cardiometabolic risk parameters

	Total MVPA (HG)			Total MVPA (CG)		
	n	**r_s**	**p**	**n**	**r_s**	**p**
Body Mass Index (kg/m^2)	48	.140	.344	30	-.554	**.001***
Fat Mass %	47	-.020	.895	30	-.451	**.012***
Skeletal Muscle Mass (kg)	47	.297	**.043***	30	.245	.191
Waist Circumference (cm)	48	.113	.445	30	-.425	**.019***
Hip Circumference (cm)	48	.139	.346	30	-.213	.258
Waist-Hip Ratio	48	.056	.706	30	-.399	**.029***
Waist-Height Ratio	48	.056	.708	30	-.455	**.011***
Six Minute Walk Test (m)	46	.102	.502	30	.409	**.025***
$_{pred}VO_2max$ (mL/kg/min)	46	.102	.502	30	.303	.103
Left grip strength (kg)	42	.070	.659	30	-.283	.130
Right grip strength (kg)	41	.189	.237	30	-.244	.194
Systolic BP (mmHg)	48	.130	.378	30	-.058	.761
Diastolic BP (mmHg)	48	.003	.985	30	-.378	**.039***
Pulse Wave Velocity (m/s)	47	-.123	.411	29	-.245	.200
Augmentation Index (%)	47	-.120	.423	29	-.159	.410
	Freedson MVPA‡ (HG)			**Freedson MVPA‡ (CG)**		
	n	**r_s**	**p**	**n**	**r_s**	**p**
Body Mass Index (kg/m^2)	48	.142	.337	30	-.527	**.003***
Fat Mass %	47	-.040	.791	30	-.411	**.024***
Skeletal Muscle Mass (kg)	47	.328	**.024***	30	.138	.466
Waist Circumference (cm)	48	.114	.441	30	-.437	**.016***
Hip Circumference (cm)	48	.139	.347	30	-.348	.060
Waist-Hip Ratio	48	.026	.858	30	-.346	.061
Waist-Height Ratio	48	.063	.669	30	-.432	**.017***
Six Minute Walk Test (m)	46	.125	.408	30	.284	.128
$_{pred}VO_2max$ (mL/kg/min)	46	.125	.408	30	.318	.087
Left grip strength (kg)	42	-.052	.745	30	-.421	**.020***
Right grip strength (kg)	41	.058	.720	30	-.276	.141
Systolic BP (mmHg)	48	.063	.669	30	-.036	.849
Diastolic BP (mmHg)	48	-.082	.582	30	-.376	**.040***
Pulse Wave Velocity (m/s)	47	-.095	.525	29	-.239	.211
Augmentation Index (%)	47	-.363	**.012***	29	-.103	.593

BP Blood Pressure **CG** Control Group **HG** Haemophilia Group **MVPA** Moderate-Vigorous Physical Activity **$_{pred}VO_2max$** Predicted Maximal Volume of Oxygen Consumption **r_s** Spearman's Rho; **†** 150 minutes of MVPA per week in total; **‡** 150 minutes of MVPA per week achieved in Freedson bouts of ≥10 minutes; *** statistically significant at α= .05 (two-tailed).**

Table 4.6b Mann Whitney U test results of fitness and cardiometabolic risk parameters compared by physical activity categories

Meeting PA guidelines via total MVPA (Yes vs. No)†	HG				CG			
	n	Mean ranks	U	p	n	Mean ranks	U	p
Body Mass Index (kg/m^2)	35 vs. 13	25.70 vs. 21.27	269.5	.330	27 vs. 3	14.52 vs. 24.33	14.0	.072
Fat Mass %	35 vs. 12	23.83 vs. 24.50	204.0	.883	27 vs. 3	14.26 vs. 26.67	7.0	**.015***
Skeletal Muscle Mass (kg)	35 vs. 12	26.70 vs. 16.13	304.5	**.021***	27 vs. 3	16.37 vs. 7.67	64.0	.117
Waist Circumference (cm)	35 vs. 13	25.46 vs. 21.92	261.0	.437	27 vs. 3	14.41 vs. 25.33	11.0	**.041***
Hip Circumference (cm)	35 vs. 13	25.51 vs. 21.77	263.0	.410	27 vs. 3	14.89 vs. 21.0	24.0	.283
Waist-Hip Ratio	35 vs. 13	24.57 vs. 24.31	230.0	.954	27 vs. 3	14.35 vs. 25.83	9.5	**.026***
Waist-Height Ratio	35 vs. 13	24.94 vs. 23.31	243.0	.718	27 vs. 3	14.43 vs. 25.17	11.5	**.041***
Six Minute Walk Test (m)	34 vs. 12	24.56 vs. 20.50	240.0	.368	27 vs. 3	16.33 vs. 8.00	63.0	.135
$_{pred}VO_2max$ (mL/kg/min)	34 vs. 12	24.56 vs. 20.50	240.0	.368	27 vs. 3	16.48 vs. 6.67	67.0	.072
Left grip strength (kg)	30 vs. 12	23.25 vs. 17.13	232.5	.146	27 vs. 3	15.20 vs. 18.17	32.5	.600
Right grip strength (kg)	29 vs. 12	23.05 vs. 16.04	233.5	.088	27 vs. 3	15.85 vs. 12.33	50.0	.554
Systolic BP (mmHg)	35 vs. 13	24.66 vs. 24.08	233.0	.898	27 vs. 3	15.26 vs. 17.67	34.0	.695
Diastolic BP (mmHg)	35 vs. 13	23.83 vs. 26.31	204.0	.585	27 vs. 3	14.48 vs. 24.67	13.0	.061
Pulse Wave Velocity (m/s)	34 vs. 13	23.10 vs. 26.35	190.5	.468	26 vs. 3	13.98 vs. 23.83	12.5	.056
Augmentation Index (%)	34 vs. 13	23.41 vs. 25.54	201.0	.634	26 vs. 3	14.21 vs. 21.83	18.5	.150
Meeting PA guidelines via Freedson MVPA (Yes vs. No)‡	**HG**				**CG**			
	n	**Mean ranks**	**U**	**p**	**n**	**Mean ranks**	**U**	**p**
Body Mass Index (kg/m^2)	9 vs. 39	20.50 vs. 25.42	139.5	.348	17 vs. 13	12.03 vs. 20.04	51.5	**.012***
Fat Mass %	9 vs. 38	16.28 vs. 25.83	101.5	.059	17 vs. 13	13.06 vs. 18.69	69.0	.086
Skeletal Muscle Mass (kg)	9 vs. 38	26.28 vs. 23.46	191.5	.585	17 vs. 13	16.06 vs. 14.77	120.0	.711
Waist Circumference (cm)	9 vs. 39	21.33 vs. 25.23	147.0	.466	17 vs. 13	12.76 vs. 19.08	64.0	.053
Hip Circumference (cm)	9 vs. 39	23.50 vs. 24.73	166.5	.815	17 vs. 13	13.35 vs. 18.31	74.0	.133
Waist-Hip Ratio	9 vs. 39	22.39 vs. 24.99	156.5	.621	17 vs. 13	13.38 vs. 18.27	74.5	.133
Waist-Height Ratio	9 vs. 39	20.06 vs. 25.53	135.5	.296	17 vs. 13	12.74 vs. 19.12	63.5	**.048***
Six Minute Walk Test (m)	9 vs. 37	25.89 vs. 22.92	188.0	.567	17 vs. 13	17.50 vs. 12.88	144.5	.157
$_{pred}VO_2max$ (mL/kg/min)	9 vs. 37	25.89 vs. 22.92	188.0	.567	17 vs. 13	17.18 vs. 13.31	139.0	.245
Left grip strength (kg)	8 vs. 34	12.69 vs. 23.57	65.5	**.022***	17 vs. 13	11.94 vs. 20.15	50.0	**.010***
Right grip strength (kg)	8 vs. 33	16.63 vs. 22.06	97.0	.262	17 vs. 13	13.21 vs. 18.50	71.5	.103
Systolic BP (mmHg)	9 vs. 39	26.50 vs. 24.04	193.5	.640	17 vs. 13	15.62 vs. 15.35	112.5	.934
Diastolic BP (mmHg)	9 vs. 39	22.61 vs. 24.94	158.5	.659	17 vs. 13	13.21 vs. 18.50	71.5	.103
Pulse Wave Velocity (m/s)	9 vs. 38	19.67 vs. 25.03	132.0	.304	16 vs. 13	13.63 vs. 16.69	82.0	.351
Augmentation Index (%)	9 vs. 38	21.17 vs. 24.67	145.5	.497	16 vs. 13	15.31 vs. 14.62	109.0	.846

BP Blood Pressure **CG** Control Group **HG** Haemophilia Group **MVPA** Moderate-Vigorous Physical Activity $_{pred}VO_2max$ Predicted Maximal Volume of Oxygen Consumption **†** 150 minutes of MVPA per week achieved in total; **‡** 150 minutes of MVPA per week achieved in Freedson bouts of ≥10 minutes; *** statistically significant at α= .05 (two-tailed).**

4.3.10 Clinical phenotype, physical fitness and cardiometabolic risk parameters

Clinical phenotypic parameters were examined in relation to fitness and cardiometabolic risk parameters in the HG using Spearman's rank order correlation analyses, and findings are presented in Table 4.7a. ABR was very weakly correlated with all physical fitness and cardiometabolic parameters. The HJHS was moderately correlated with WHR, but correlations with all other BC variables were weak. Weak, inverse correlations were demonstrated between the HJHS and 6MWT. Upon further analysis, the 6MWT was weakly correlated with individual component scores for the knee (r_s= -.129; p=.398), and ankle (r_s= -.159; p=.296). A weak, inverse correlation was found between the HJHS and right grip strength, whilst it was moderately correlated with left grip strength. When further analysed, left elbow component scores were moderately correlated with left grip strength (r_s= -.470; p= .002; n= 41), and weakly correlated with left arm SMM (r_s= -.336; p= .022; n= 46). Left arm SMM and left grip strength were moderately correlated (r_s= .542; p= .000; n= 43). Individual right elbow component scores were moderately correlated with right grip strength (r_s= -.572; p= .000; n= 40), and weakly correlated with right arm SMM (r_s= -.372; p= .011; n= 46). Right arm SMM and right grip strength were moderately correlated (r_s= .616; p= .000; n= 42).

The HJHS was weakly correlated with BP. A moderate correlation between the HJHS and PWV was demonstrated (Figure 4.4a), whilst a weak, inverse correlation was found between the HJHS and AIx (Figure 4.4b). The age at which prophylaxis was commenced was weakly correlated with BMI, FM%, SMM, WC and HC, and moderately correlated with WHR and WHtR. A weak, inverse correlation was found between the age at which prophylaxis was commenced and the 6MWT, whilst moderate, inverse correlations were found between the age at which prophylaxis was commenced and grip strength. Age at which prophylaxis was commenced was weakly correlated with BP. A strong, positive correlation was demonstrated between the age at which prophylaxis was commenced and PWV (Figure 4.5a), whilst a weak, inverse correlation was demonstrated with AIx (Figure 4.5b). There were no significant differences in ABR or the HJHS between participants with impaired balance compared to those with normal balance [ABR: n= 18 vs. 33, mean ranks: 28.14 vs. 24.83 (respectively); U= 258.5; p= .442; HJHS: n= 17 vs. 29, mean ranks: 28.12 vs. 20.79 (respectively); U= 168.0; p= .074]. The age at which prophylaxis was commenced was significantly lower in participants with normal balance compared to those with impaired balance [n= 26 vs. 14, mean ranks: 16.79 vs. 27.39 (respectively); U= 85.5; p= .005].

There were no significant differences in ABR between participants with or without formally diagnosed HTN in the HG [n= 12 vs. 41; mean ranks: 27.46 vs. 26.87 (respectively); U= 251.5; p= .906]. The HJHS was higher in those with HTN, but differences were not significant [n= 11 vs. 37; mean ranks: 31.55 vs. 22.41; U= 281.0; p= .057]. The age at which prophylaxis was commenced was significantly older in adults with HTN compared to those without HTN [n= 9 vs. 32; mean ranks= 30.72 vs. 18.27 (respectively); U= 231.5; p= .004]. Clinical phenotypic data were not statically analysed in participants with IR due to the limited sample size (n= 3), however the range of values were as follows: ABR (0-3); HJHS (27-34); age at which prophylaxis was commenced (38-63). The sample

size was also too small to statistically analyse for participants with HLD (n=4), thus the range of values were as follows: ABR (0-2); HJHS (21-54); age prophylaxis commenced (48-63).

Due to the potentially elevated cardiometabolic risk in participants with a history of HCV or HIV, physical fitness and cardiometabolic risk parameters were compared by HCV, HIV and co-infection status using the Mann-Whitney U test. Findings are presented in Table 4.7b. Participants with a previous history of HCV had significantly lower SMM, and significantly higher WHR and WHtR compared to participants with no previous history of HCV. BP and PWV were also significantly higher in participants with a previous history of HCV. AIx and the remaining parameters of BC and physical fitness were not significantly different between groups. Participants who were HIV positive had significantly lower SMM and HC compared to participants who were HIV negative. WHR, SBP and PWV was significantly higher in participants who were HIV positive compared to those who were HIV negative. The remaining parameters of BC, fitness and vascular health were not significantly different between groups. WHR was significantly higher in participants who were co-infected with both HIV and HCV, but BMI, SMM and HC were significantly lower compared to participants without a history of co-infection. There were no significant differences between these groups for physical fitness, vascular health or the remaining BC parameters.

Of 12 participants in the HG who had formally diagnosed HTN, two had a normal BMI, whilst the remaining participants were overweight or obese. Participants with HTN had a significantly higher BMI than those who did not have HTN [n= 12 vs. 41; mean ranks= 34.96 vs. 24.67 (respectively); U= 341.5; p= .042]. All 12 participants had a previous history of HCV, and six had a history of HIV coinfection. Of three participants with IR, all were classified as overweight by BMI. All three had a previous history of HCV, and one participant had HIV coinfection. Of four participants with HLD, all were overweight or obese according to BMI. All had a previous history of HCV, and two had HIV coinfection.

Table 4.7a: Spearman rank order correlation analyses between clinical phenotype, physical fitness and cardiometabolic risk parameters

	ABR†		HJHS‡		Age prophylaxis commenced¶	
	r_s	p	r_s	p	r_s	p
Body Mass Index (kg/m^2)	.050	.720	.121	.411	.206	.197
Fat Mass %	.016	.911	.268	.068	.378	**.016***
Skeletal Muscle Mass (kg)	-.136	.338	-.329	**.024***	-.350	**.027***
Waist Circumference (cm)	-.027	.847	.251	.085	.333	**.033***
Hip Circumference (cm)	-.027	.846	.125	.396	.112	.486
Waist-Hip Ratio	.023	.873	.417	**.003***	.544	**.000***
Waist-Height Ratio	.025	.858	.312	**.031***	.482	**.001***
Six Minute Walk Test (m)	.069	.633	-.140	.359	-.302	.061
$_{pred}VO_2max$ (mL/kg/min)	.069	.633	-.140	.359	-.302	.061
Left grip strength (kg)	-.198	.193	-.434	**.005***	-.479	**.003***
Right grip strength (kg)	-.063	.682	-.332	**.037***	-.494	**.003***
Systolic BP (mmHg)	.070	.617	.064	.666	.150	.349
Diastolic BP (mmHg)	-.128	.360	.350	**.015***	.276	.080
Pulse Wave Velocity (m/s)	.101	.479	.532	**.000***	.859	**.000***
Augmentation Index (%)	-.106	.458	-.098	.517	-.242	.137

ABR Annualised Bleed Rate **BP** Blood Pressure **HJHS** Haemophilia Joint Health Score **$_{pred}VO_2max$** Predicted Maximal Volume of Oxygen Consumption **r_s** Spearman's Rho; **†** Body Mass Index, Waist Circumference Indices and Blood Pressure Indices n= 53; Fat Mass % and Skeletal Muscle Mass n= 52; Six Minute Walk Test and $_{pred}VO_2max$ n= 50; Pulse Wave Velocity and Augmentation Index n= 51; Left grip strength n= 45; Right grip strength n= 44**; ‡** HJHS n= 48; Body Mass Index, Waist Circumference Indices and Blood Pressure Indices n= 48; Fat Mass % and Skeletal Muscle Mass n= 47; Six Minute Walk Test and $_{pred}VO_2max$ n= 45; Pulse Wave Velocity and Augmentation Index n= 46; Left grip strength n= 45; Right grip strength n= 44; ¶ Age prophylaxis commenced n= 41; Body Mass Index, Waist Circumference Indices and Blood Pressure Indices n= 41; Fat Mass % and Skeletal Muscle Mass n= 40; Six Minute Walk Test and $_{pred}VO_2max$ n= 39; Pulse Wave Velocity and Augmentation Index n= 39; Left grip strength n= 36; Right grip strength n= 35; *** statistically significant at α= .05 (two-tailed).**

Table 4.7b Mann Whitney U test results of fitness and cardiometabolic risk parameters compared by HCV and HIV categories

	HCV (Previous history vs. No history)				HIV (Positive vs. Negative)				Co-infection (Yes vs. No)			
	n	Mean ranks	U	p	n	Mean ranks	U	p	n	Mean ranks	U	p
Body Mass Index (kg/m^2)	38 vs. 15	28.29 vs. 23.73	236.0	.333	14 vs. 39	21.75 vs. 28.88	199.5	.138	14 vs. 24	14.18 vs. 22.60	93.5	**.023***
Fat Mass %	37 vs. 15	28.58 vs. 21.37	200.5	.119	14 vs. 38	24.64 vs. 27.18	240.0	.591	14 vs. 23	15.61 vs. 21.07	113.5	.138
Skeletal Muscle Mass (kg)	37 vs. 15	23.41 vs. 34.13	392.0	**.021***	14 vs. 38	16.89 vs. 30.04	131.5	**.006***	14 vs. 23	13.86 vs. 22.13	89.0	**.024***
Waist Circumference (cm)	38 vs. 15	29.46 vs. 20.77	191.5	.065	14 vs. 39	27.71 vs. 26.74	283.0	.840	14 vs. 24	17.93 vs. 20.42	146.0	.520
Hip Circumference (cm)	38 vs. 15	26.87 vs. 27.33	290.0	.921	14 vs. 39	20.00 vs. 29.51	175.0	**.048***	14 vs. 24	13.79 vs. 22.83	88.0	**.015***
Waist-Hip Ratio	38 vs. 15	32.26 vs. 13.67	85.0	**.000***	14 vs. 39	38.36 vs. 22.92	432.0	**.001***	14 vs. 24	24.68 vs. 16.48	240.5	**.027***
Waist-Height Ratio	38 vs. 15	30.75 vs. 17.50	142.5	**.005***	14 vs. 39	29.93 vs. 25.95	314.0	.407	14 vs. 24	18.71 vs. 19.96	157.0	.754
Six Minute Walk Test (m)	35 vs. 15	24.77 vs. 27.20	288.0	.589	12 vs. 38	26.75 vs. 25.11	243.0	.733	12 vs. 23	19.25 vs. 17.35	153.0	.619
$_{pred}VO_2max$ (mL/kg/min)	35 vs. 15	24.77 vs. 27.20	288.0	.589	12 vs. 38	26.75 vs. 25.11	243.0	.733	12 vs. 23	19.25 vs. 17.35	153.0	.619
Left grip strength (kg)	32 vs. 13	21.53 vs. 26.62	255.0	.239	11 vs. 34	16.36 vs. 25.15	114.0	.055	11 vs. 21	12.82 vs. 18.43	75.0	.113
Right grip strength (kg)	31 vs. 13	22.47 vs. 22.58	202.5	.979	11 vs. 33	17.36 vs. 24.21	125.0	.130	11 vs. 20	12.36 vs. 18.00	70.0	.104
Systolic BP (mmHg)	38 vs. 15	30.25 vs. 18.77	161.5	**.015***	14 vs. 39	34.61 vs. 24.47	379.5	**.031***	14 vs. 24	22.96 vs. 17.48	216.5	.144
Diastolic BP (mmHg)	38 vs. 15	31.28 vs. 16.17	122.5	**.001***	14 vs. 39	33.21 vs. 24.77	360.0	.079	14 vs. 24	21.36 vs. 18.42	194.0	.445
Pulse Wave Velocity (m/s)	36 vs. 15	32.92 vs. 9.40	21.0	**.000***	13 vs. 38	37.54 vs. 22.05	397.0	**.001***	13 vs. 23	22.58 vs. 16.20	202.5	.081
Augmentation Index (%)	36 vs. 15	24.10 vs. 30.57	338.5	.156	13 vs. 38	22.15 vs. 27.32	197.0	.279	13 vs. 23	17.27 vs. 19.20	133.5	.603

BP Blood Pressure **HCV** Hepatitis C Virus **HIV** Human Immunodeficiency Virus **$_{pred}VO_2max$** Predicted Maximal Volume of Oxygen Consumption; *** statistically significant at α= .05 (two-tailed).**

Figure 4.4a: Scatterplot of Haemophilia Joint Health Score and Pulse Wave Velocity

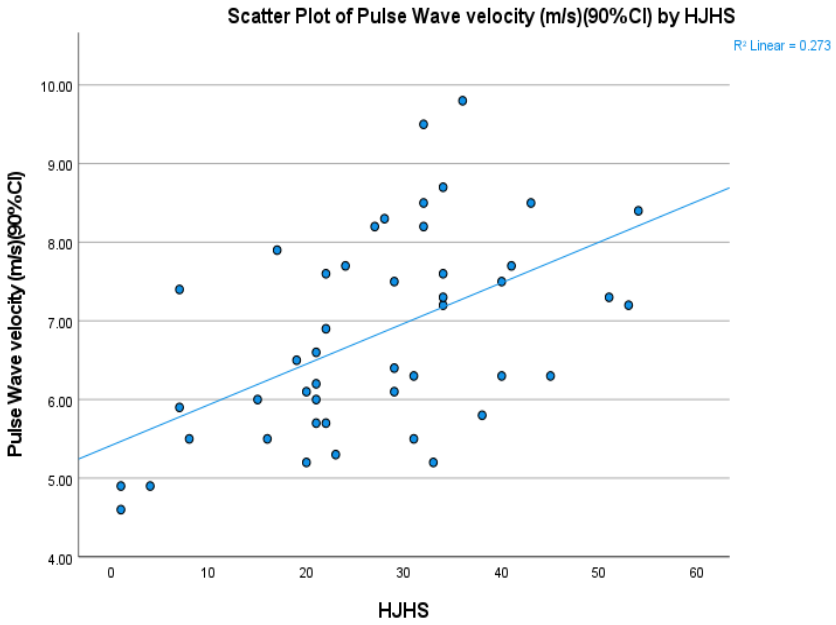


Figure 4.4b: Scatterplot of Haemophilia Joint Health Score and Augmentation Index

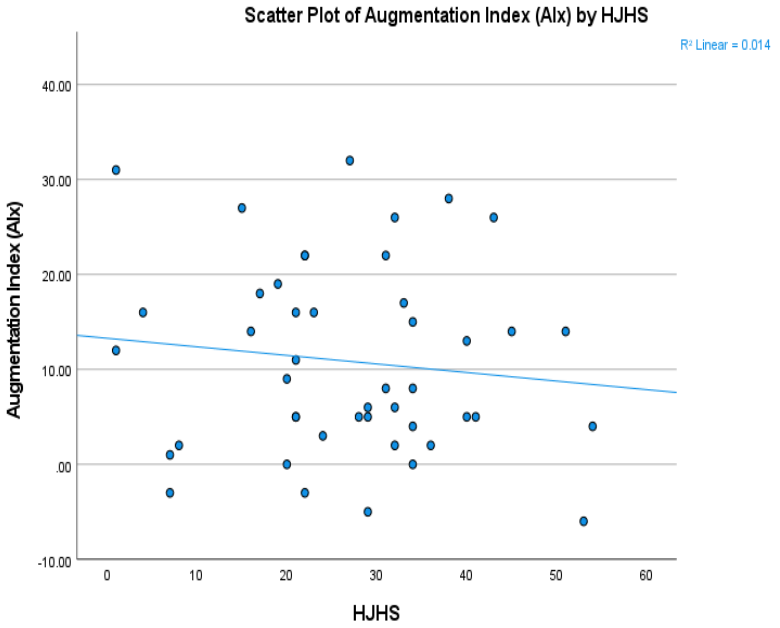


Figure 4.5a: Scatterplot of Age Prophylaxis Commenced and Pulse Wave Velocity

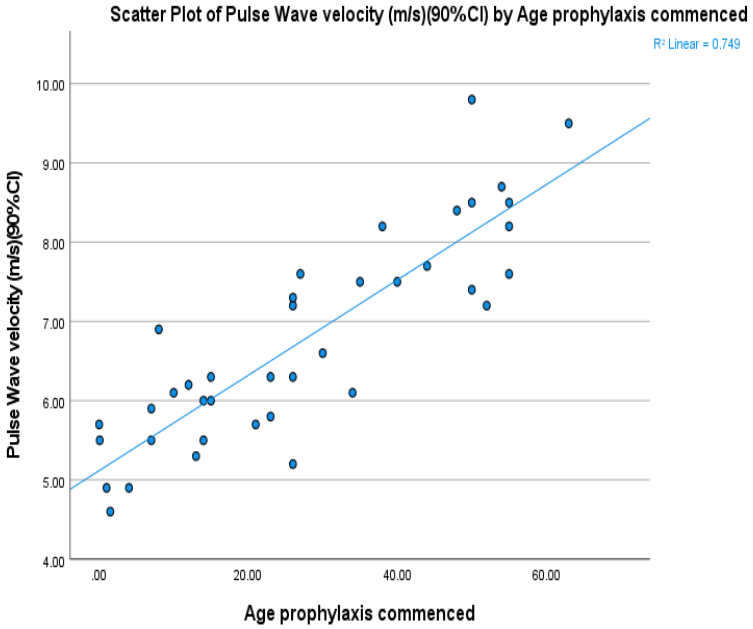
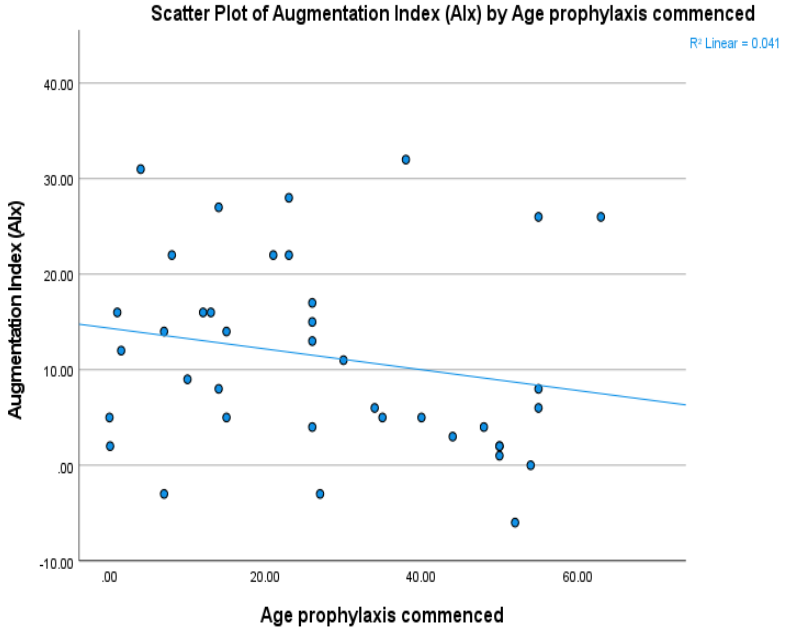


Figure 4.5b: Scatterplot of Age Prophylaxis Commenced and Augmentation Index



4.4 Discussion

This study aimed to examine parameters of physical fitness and cardiometabolic risk in adult PwMSH, and additionally examine these parameters in relation to age, PA and clinical phenotype. Increased abdominal obesity, decreased physical fitness and a relatively high prevalence of cardiometabolic disorders were found in PwMSH compared to adults without haemophilia, which is suggestive of a potentially heightened chronic health risk in ageing PwMSH.

4.4.1 Anthropometry and body composition

A high prevalence of overweight and obesity measured by BMI was found in adult PwMSH in the present study (66%). This prevalence was comparable to adults without haemophilia, and similar to reports of overweight and obesity from the general male adult population in Ireland (63-66%) (Ward et al., 2009, Healthy Ireland, 2019). Furthermore, this prevalence was within similar ranges of overweight and obesity reported in PwH (31-68%), (Hofstede et al., 2008, Majumdar et al., 2010, Tuinenburg et al., 2013, McNamara et al., 2014, Kahan et al., 2017, Wilding et al., 2018, Yıldız et al., 2019). FM% and SMM were not significantly different between PwMSH and controls in the present study, which is in keeping with findings reported by Putz et al. (2021) who measured these variables using the same BIA device. Anthropometric indices involving WC were significantly higher in PwMSH compared to controls, although the prevalence of increased WC in PwMSH (54.7%) was comparable to that reported in the general male adult population of Ireland (56%) (Healthy Ireland, 2015). Age-related influences on BC were not apparent when measured by BMI in the present study. However, older adults demonstrated significantly increased central adiposity and lower SMM compared to younger adults in both study groups, which is not surprising considering the known effects of ageing on BC (JafariNasabian et al., 2017). Overall, the findings suggest that abdominal obesity, a more sensitive predictor of cardiometabolic risk (Klein et al., 2007, WHO, 2011, Després, 2012, Ashwell et al., 2012, Jayedi et al., 2020), may pose a significant health concern for ageing PwMSH, similarly to the general population.

Interestingly, FM% and anthropometric indices involving WC were significantly lower in controls who achieved PA guidelines, however this trend was not demonstrated in PwMSH. Higher intensity PA is associated with a greater impact on weight loss and weight management (Donnelly et al., 2009, Cox, 2017). Considering PwMSH were significantly less active in MVPA than controls, particularly via Freedson bouts of sustained MVPA ≥10 minutes, it may be that the intensity and duration of MVPA achieved by PwMSH is not sufficient to have a substantial impact on weight. This may potentially be related to the impact of lower limb haemophilic arthropathy on exercise tolerance. Furthermore, adequate PA contributes to the maintenance of SMM with age, and this was reflected in the present study as PwMSH who achieved PA guidelines had significantly higher SMM compared to participants who did not achieve guidelines. The risk of sarcopenia associated with ageing may be accelerated in older PwMSH due to muscular atrophy associated with advanced haemophilic arthropathy. Therefore, these findings highlight the benefit of adequate PA for maintaining and potentially increasing SMM in PwMSH.

ABR was not correlated with BC in the present analysis, which was also reported by Tuinenburg et al. (2013). However, the HJHS and age at which prophylaxis was commenced were weakly to moderately correlated with WC indices. This highlights a potentially important role for weight management education throughout the life span in PwMSH to optimise joint health and alleviate pain. Nutritional intake was not assessed in this study, but may offer additional important insights regarding the relationship between PA, BC and weight management in PwMSH in future studies.

There were no significant differences in BC parameters by type and severity of haemophilia in the present study. Previous studies in adults and children with haemophilia have demonstrated conflicting reports of the impact of haemophilia type and severity on BMI. Some have indicated no significant differences between mild, moderate or severe haemophilia (Majumdar et al., 2010), whilst others have found severe haemophilia to be associated with increased rates of overweight and obesity (Hofstede et al., 2008, Revel-Vilk et al., 2011). The analysis of haemophilia type and severity on BC was limited in the present analysis due to the small and unequal sample of adults with moderate haemophilia compared to severe haemophilia, and the lack of a mild haemophilia cohort. Therefore, further studies on BC in PwH of all severities are warranted.

HCV and HIV status appeared to influence BC measurements in the present study. A proportion of this group who were co-infected with HCV and HIV had a significantly lower BMI compared to participants who were not co-infected. SMM was significantly lower in participants with a history of HCV, HIV and co-infection, compared to those with no history of comorbid disease; thus, BMI may underestimate overweight and obesity in PwMSH who have a history of HCV and HIV. This, however, may also be confounded by older age and more severe muscular atrophy associated with haemophilic arthropathy in this cohort. Furthermore, both WHR and WHtR were significantly higher in participants with a history of HCV, which may reflect potentially increased weight gain post-HCV treatment and eradication, which has been noted in the general population of HCV who were successfully treated (Mostafa et al., 2010, Lonardo et al., 2014, Do et al., 2020). Additionally, HC was significantly lower despite similar WC measurements in participants with HIV co-infection, therefore the significantly higher WHR in these individuals may have been predominantly mediated by a reduced HC. This could be due to potential lipodystrophy which is associated with antiretroviral treatment for HIV (Carr, 2003, Nduka et al., 2016). WC and WHtR may therefore be more reliable measures of adiposity in PwMSH as the influence of peripheral muscular atrophy associated with various complications of haemophilia and age may affect these measures. Further examination of the validity of anthropometric measures of BC compared to criterion measures in PwH of varying age, type and severity is warranted. This would help to ascertain the most accurate measure of BC for the longitudinal assessment of overweight and obesity in the ageing haemophilia population.

4.4.2 Physical fitness parameters

Decreased functional aerobic capacity, $_{pred}VO_2max$, dominant hand grip strength and balance were demonstrated in adult PwMSH compared to controls in the present study. 6MWT scores were similar to those reported in previous studies of adults with haemophilia (Salim et al., 2016, Castaño et al.,

2017, Deniz et al., 2022). Age did not appear to influence 6MWT scores in either group, although scores appeared to be somewhat higher in adults achieving PA guidelines in both groups, despite non-significant differences. The 6MWT was weakly correlated with ABR, HJHS and age at which prophylaxis was commenced. Despite a standardised protocol for the administration of the 6MWT in the present study, the pace at which participants walk during the test is self-selected. There may also be a tendency for PwMSH not to push themselves to maximal exertion due to a lack of experience in higher intensity PA, or fear of pain, injury or bleeds, which may limit the interpretation of these findings. The interpretation of $_{pred}VO_2max$ based off 6MWT scores in the HG therefore also has inherent limitation. Further studies are required to ascertain the feasibility of more objective measurements of functional capacity and CRF in adults with haemophilia, in order to improve the assessment methods and provide more accurate insights of their relationship between functional capacity and CRF with lower limb joint health, function and PA.

Grip strength in PwMSH was similar in the present study to that reported by Goto et al. (2015) which was measured using similar methods. Grip strength of the dominant hand was significantly reduced in PwMSH compared to controls, potentially reflecting the impact of elbow joint arthropathy on muscular strength, considering grip strength was also moderately correlated with the HJHS elbow component scores and upper limb SMM. This is in keeping with evidence of reduced muscular strength associated with higher severities of haemophilic arthropathy (Stephensen et al., 2012). Grip strength also reduced with age in both groups, which may have further implications for frailty in ageing PwMSH who have significant haemophilic arthropathy. Additionally, the impact of treatment regimen on grip strength warrants further exploration in light of the moderate correlation identified between grip strength and the age at which prophylaxis was commenced. Light intensity strengthening programmes have been shown to safely increase strength in PwH without adverse events (Wagner et al., 2020), and could have the potential to reduce accelerated decreases in physical strength in ageing PwMSH. It has also been suggested that strengthening exercise may reduce the frequency of bleeds due to improved stability and support of joint structures, although further research of this is warranted (Koch et al., 1982, Greene and Strickler, 1983, Pelletier et al., 1987, Tiktinsky et al., 2002, Gomis et al., 2009, Siqueira et al., 2019).

Higher rates of impaired balance were identified in PwMSH compared to controls in the present study. Previous literature also demonstrated significantly impaired balance in PwH due to the impact of haemarthroses and haemophilic arthropathy on lower limb proprioception (Gallach et al., 2008, Fearn et al., 2010, Czepa et al., 2012, Souza et al., 2013). Those with impaired balance were significantly older, had a significantly higher HJHS and commenced prophylaxis at a significantly later age. The considerable prevalence of reduced bone mineral density in the present sample (~42% of 38 adults with available data; Table 4.3.2a) is concerning in light of the high rates of impaired balance and potentially reduced lower limb strength found in this group of PwMSH. An increased risk of falls, falls-related injuries and associated complications in older PwMSH could be particularly difficult to treat and manage in light of bleeds and haemophilic arthropathy. PA did not appear to impact balance or grip strength in the present study, however the use of the ActiGraph as a measure

of habitual PA may have limited this analysis, considering specific types of exercise such as strength and balance training, which affect strength and balance parameters, cannot be reflected accurately by the ActiGraph output. A more detailed assessment of strength, balance and falls risk was not feasible for the present study due to the limited project timeframe, but warrants further examination in this cohort.

4.4.3 Vascular health parameters

There were no significant differences between PwMSH and controls in resting BP measurement in the present study, and there were no apparent influences of age or PA on BP in either group. Weak, inverse correlations were identified between vascular health parameters and MVPA. Interestingly, HCV and HIV status were significantly associated with higher resting BP and aortic arterial stiffness measurement via PWV. HCV and HIV are associated with an increased cardiovascular risk, therefore the vascular health of affected PwMSH may require regular screening and monitoring.

Measurements of arterial stiffness using PWV and AIx in PwMSH were similar in comparison to normative values generated in healthy populations which range from 5.86-10.3 (± 1.3-2.0) m/s for PWV (Mitchell et al., 2004, Mattace-Raso et al., 2010, Elias et al., 2011, Díaz et al., 2014) and -2-28 (± 8.0-12.5) for AIx (McEniery et al., 2005, Janner et al., 2010). There was no difference in PWV between the HG and CG, supporting suggestions that PwH may not be inherently protected from atherosclerosis and associated cardiovascular complications (Sartori et al., 2008, Zwiers et al., 2012). Correlations were strong between age and PWV in both groups, which is also in keeping with previous reports in the general population (Mitchell et al., 2004, Mattace-Raso et al., 2010, Díaz et al., 2014). AIx, which represents an estimate of peripheral arterial stiffness, was significantly higher in the HG compared to the CG. Although correlations were weak between AIx and age in the HG, contradicting trends in AIx with age were demonstrated, whereby age was inversely correlated with AIx in the HG, yet positively correlated with AIx in the CG (which is in keeping with previous literature in the general population) (McEniery et al., 2005, Janner et al., 2010). Similar patterns in trends were also demonstrated between PWV and AIx with the HJHS and the age at which prophylaxis was commenced. This is interesting in light of recent evidence regarding vascular remodelling associated with haemarthroses in animal studies of haemophilia (Acharya et al., 2011, Bhat et al., 2015, Cooke et al., 2019, Gopal et al., 2021). The present assessment was limited by the use of estimated measures of arterial stiffness via brachial-cuff oscillometry, therefore future studies using criterion measures are recommended to further examine the relationship between arterial stiffness, bleeding phenotype and joint health, as well as the potential influence of age on these parameters.

4.4.4 Cardiometabolic disorders

The prevalence of formally diagnosed HTN, IR and HLD was higher in adult PwMSH compared to adults without haemophilia in the present study, with a considerable proportion of participants having more than one cardiometabolic disorder. Although these findings should be interpreted with caution due to the small sample size of both study groups, the rate of HTN was higher (22.6%) in PwMSH

compared to the national male average (13.0%) in Ireland (Healthy Ireland, 2019). This is in keeping with previous reports of a higher prevalence of HTN in PwH compared to the general population (Street et al., 2006, Mauser-Bunschoten et al., 2009, Fransen van de Putte et al., 2012a, Samuelson Bannow et al., 2019). The prevalence of IR and HLD were slightly lower compared to national male average in Ireland (Healthy Ireland, 2019), which again should be interpreted with caution. Consequently, formal statistical analyses were mostly limited, however a number of factors were apparent in adults with cardiometabolic disorders. All PwMSH with cardiometabolic disorders were older (≥45 years), overweight or obese, and also had comorbid HCV or HIV co-infection. There was no clear influence of MVPA on rates of cardiometabolic comorbidity, however the small sample size may again limit this interpretation, as physical inactivity is an established risk factor for cardiometabolic morbidity and mortality (Piercy et al., 2018). Furthermore, the HJHS and the age at which prophylaxis was commenced were significantly associated with HTN status. Interestingly, vascular remodelling in haemophilic joints has been associated with an increased prevalence of HTN in PwH, potentially contributing to the higher rates of HTN noted compared to the general population (Barnes et al., 2017, Samuelson Bannow et al., 2019). Despite conflicting evidence in the literature on the prevalence of cardiometabolic morbidity and mortality compared to the general population, findings from the present study suggest that ageing PwMSH are at a potentially increased risk of developing cardiometabolic risk factors and diseases. This risk may in part be associated with comorbid HCV or HIV history particularly in older adults, which may warrant special consideration for the comprehensive care of affected PwMSH as they age.

4.4.5 Limitations

A number of additional inherent limitations in the design and analysis of this study, other than those already discussed, warrant acknowledgement. Despite the best efforts to recruit as many participants as possible over a lengthy recruitment period, the small sample size ultimately recruited may have increased the risk of a type II error in the statistical analysis. This is a common limitation of many studies in haemophilia research, considering it is a rare genetic disorder. Further recruitment to increase the sample size was also impacted by Covid-19 pandemic which was beyond control. Furthermore, the convenience sampling methods used may have increased the risk of the study groups not being representative of their respective populations. Specifically, participants of the CG were predominantly recruited from a healthcare work setting and may have had greater health literacy and awareness compared to the HG. Non-response bias could also not be measured as demographics and characteristics of non-responders were inherently not obtainable. Causation or temporality cannot be inferred between the variables analysed in relation to each other due to the cross-sectional nature of the study design, however the present study does offer insights which may be explored in further detail in future appropriately designed studies. The potential to obtain CRF fitness data for the HG was disrupted by the Covid-19 pandemic, however the use of estimated $_{pred}VO_2max$ based off normative data has inherent limitation. The accuracy of the regression equation used to predict VO_2max from a small cohort is also limited. Lastly, the measurement of resting BP may not have been the most reliable estimate of general BP in this assessment. A 24-hour BP

assessment, which would have been superior, was not feasible for the present study, but may be considered for further investigation in future research.

4.5 Conclusion

This study demonstrated evidence of increased adiposity, cardiometabolic risk and reduced physical fitness in adult PwMSH compared to controls, which may have significant implications on long-term health risk in the ageing haemophilia population. PA did not appear to influence BC in PwMSH compared to adults without haemophilia, which may reflect the burden of haemophilic arthropathy on exercise tolerance. Therefore, weight loss and weight management interventions with more of an emphasis on diet, rather than high intensity exercise programmes, may be more successful in addressing the issue of increased adiposity in PwMSH. Age, comorbid disease status and clinical phenotypic features of haemophilia may also influence BC, vascular health, cardiometabolic risk and physical fitness, which warrants further examination in future studies. The mechanisms of cardiometabolic risk, such as obesity and HTN, also warrant further investigation. Lastly, longitudinal studies examining BC, physical fitness and cardiometabolic risk, and how these variables relate to variation in clinical phenotype in PwH of all ages are recommended. This would help to inform guidelines and interventions for healthy ageing in PwH, who face additional long-term health challenges compared to the general population. This is especially important in light of the increasing life expectancy in the global haemophilia population.

Chapter 5: Study III: Barriers to physical activity in adults with moderate and severe haemophilia

Section I: Study IIIa: An investigation of barriers to physical activity in adults with moderate and severe haemophilia

5I.1 Introduction

Study I of this thesis found that adult people with moderate and severe haemophilia (PwMSH) were significantly less physically active compared to adults without haemophilia. In Study II, abdominal obesity and decreased physical fitness were significantly higher in PwMSH. Other cardiometabolic risk factors including hypertension, insulin resistance and hyperlipidaemia were also prevalent. Physical Activity (PA) is associated with numerous health benefits which are influenced by the volume and intensity of regular PA undertaken (Piercy et al., 2018, Bull et al., 2020).

Barriers to PA present difficulties for sufficient PA participation, inhibiting the potential to reap the numerous associated health benefits. Barriers may be multifaceted and the relationship between attitudes to PA, PA behaviours and other lifestyle factors, such as diet, is complex (Vaughan et al., 2018). In the general population, non-modifiable factors such as age and gender may affect individual tendencies to initiate and maintain PA throughout the lifespan (Seefeldt et al., 2002). A wide range of modifiable barriers to PA may vary across the lifespan, and include: social influences from family and peers; limited access to PA resources, including environmental and financial barriers; a lack of time; a lack of skill; pain; physical disability; limited health literacy; and intrapersonal barriers such as low motivation and low self-esteem (Seefeldt et al., 2002, Allender et al., 2006, Franco et al., 2015, Spiteri et al., 2019). Fear of injury or harm from PA may also concern older adults and those who are medically vulnerable (Franco et al., 2015, Spiteri et al., 2019). Many of these barriers have also been associated with poor adherence to PA and dietary interventions in adults with obesity (Burgess et al., 2017).

Barriers to PA that are common amongst the general population may also affect PwMSH. The above-mentioned findings of Study I would suggest PwMSH experience more barriers to PA than the general population, which may be due to various comorbidities and complications that are associated with haemophilia. A US survey of youths with haemophilia found that 60% avoided PA in order to prevent bleeds and manage their haemophilia, with only 27% using exercise to prevent bleeds and complications (Nazzaro et al., 2006). Haemophilia-specific barriers, in addition to common general barriers to PA, may result in lower PA participation and ultimately lead to an increased long-term health-risk in PwMSH compared to the general population. Therefore, the identification of barriers to PA in PwMSH could be useful to inform and optimise health interventions to effectively address physical inactivity.

A small number of qualitative studies to date have reported on some barriers to PA in adults with haemophilia (Flaherty et al., 2018, McLaughlin et al., 2021). To date, no study has quantitatively

examined the relationship between barriers to PA with age, body composition, current PA levels or clinical phenotypic parameters in PwMSH. The potential side effects of treatments for comorbid Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) may also influence barriers to PA, but this not been proven to date.

5I.1.1 Aim

The primary aim of this study is to determine barriers to PA in adult PwMSH. The secondary aim is to examine barriers to PA in relation to age, body composition, PA and clinical phenotype.

5I.1.2 Objectives

5I.1.2.1 Primary objective

1) To compare barriers to PA between adult PwMSH and adults without haemophilia.

5I.1.2.2 Secondary objectives

1) To determine the relationship between age and barriers to PA in both groups.

2) To determine the relationship between body composition and barriers to PA in both groups.

3) To determine the relationship between objectively measured PA and barriers to PA in both groups.

4) To determine the relationship between clinical phenotypic parameters and barriers to PA in PwMSH.

5I.2 Methodology

5I.2.1 Study design and setting **(See sections 2.2-2.4)**

This cross-sectional study was conducted between April 2018- March 2020. The haemophilia group (HG) were recruited via convenience sampling methods from the National Coagulation Centre, St. James's Hospital Dublin. The control group (CG) were recruited from the staff and student populations of St. James's Hospital, Trinity College Dublin and Tallaght University Hospital. Research assessments were conducted at the Clinical Research Facility, St. James's Hospital. Ethical approval was obtained (Appendix IV).

5I.2.2 Participant recruitment **(See section 2.5)**

People with haemophilia were screened by the clinical research team for study eligibility during routine outpatient clinics. The HG included male participants ≥18 years with clinically diagnosed moderate (1-5%) or severe (<1%) Factor VIII or Factor IX deficiency, commonly known as Haemophilia A (HA) and Haemophilia B (HB), respectively. Individuals who had active inhibitors, a lack of capacity to provide informed consent, acute medical issues, non-resolved bleeds or who were non-ambulatory were excluded. Healthy male controls ≥18 years without haemophilia or acute,

unstable medical issues were invited to participate in this study via an email and poster campaign. Individuals who lacked capacity to provide informed consent or who had neuro-musculoskeletal disorders, HCV or HIV were excluded. Individuals who expressed interest in the study were given the relevant Participant Information Leaflet to read (Appendix VIII). They were contacted one week later to determine study enrolment. Participants were scheduled for the research assessment at a time and date most convenient for them. Informed, written consent was obtained (Appendix IX).

5I.2.3 Demographics and Outcome Measures

5I.2.3.1 Demographic information

The age of both groups was documented. Haemophilia type and severity, treatment regimen and product type, the age at which prophylaxis was commenced (where applicable), inhibitor history, HCV and HIV history were also recorded in the HG.

5I.2.3.2 Outcome measures

The following outcome measures were assessed to fulfil the aims and objectives of this study:

- Bleeding phenotype was examined by calculating the ***Annualised Bleeding Rate (ABR)*** (See section 2.6.2.1).
- Joint health was examined using the participants' most recent ***Haemophilia Joint Health Score (HJHS; version 2.1)*** (See section 2.6.2.2).
- Anthropometry and body composition were measured by ***height, weight, Body Mass Index (BMI), waist circumference (WC) and waist-height ratio (WHtR)*** (See section 2.6.5.1).
- PA was objectively measured over one week using the ***ActiGraph GT3X-BT accelerometer***, and raw data were analysed using the ActiLife software (See section 2.6.3.1).
- Participants completed the ***Barriers to Being Active Quiz (BBAQ)*** (Appendix XV) to determine barriers to PA. The questionnaire consists of 21 statements related to specific barrier domains. Participants are asked how likely they are to say a statement about themselves, and to rate it using a Likert scale. Barrier domains include: lack of time; social influence; lack of energy; lack of willpower; fear of injury; lack of skill; lack of resources. The BBAQ defines individual barrier domain scores ≥5 as 'critical barriers' to PA (See section 2.6.6.2).
- PA was objectively measured over one week using the ***ActiGraph GT3X-BT accelerometer (ActiGraph Corp, Pensacola, Florida, USA)*** (See section 2.6.3.1). Raw data were downloaded cleaned and analysed using the ActiLife software. PA was classified according to achievement of PA guidelines via the total amount of MVPA undertaken per week, as well as MVPA achieved via Freedson bouts (i.e. bouts of MVPA lasting ≥10 minutes) (Bull et al., 2020).

5I.2.4 Statistical methods

Statistical analysis was conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.). The distribution of data was assessed using a combination of the Shapiro-Wilk test and visual inspection of histograms, normal Q-Q plots and box and whisker plots. Continuous variables are described as mean ± standard deviation and/ or median and interquartile range (IQR: Q1, Q3). Continuous variables were compared between two groups using the Mann-Whitney U test. This test assumes the data from both categories follow an approximately similarly shaped distribution for the comparison of median values to be interpreted. Mean ranks are reported and interpreted where the distribution of data between categories was not similar. The Kruskal-Wallis H test was used to compare continuous variables between more than two groups. Dunn's post hoc pairwise comparisons were generated for the Kruskal-Wallis H test where results were statistically significant. Continuous variables were compared by haemophilia type and severity. Moderate HA and HB were combined due to the small sample size in these groups. BBAQ domain scores were compared by haemophilia type and severity (severe HA vs. severe HB vs. moderate HA/HB); age (≥45 vs. <45 years); WHtR (increased vs. normal); achievement of PA guidelines in both the total duration of Moderate-Vigorous PA (MVPA) per week and MVPA achieved via Freedson bouts (i.e. MVPA ≥10 minutes); HCV history (previous history and successfully treated vs. no history); and HIV status (positive vs. negative). Categorical variables are described as frequencies and percentages. Critical barriers for each domain were categorised (i.e. critical vs. not critical). Chi-square tests of association were carried out between critical barrier domains and study groups. Fisher's exact test was run where expected cell counts were less than five. Missing data were excluded from analyses and are highlighted throughout the text, tables and figures with accompanying reasons. Statistical significance was considered at alpha (α)= .05 (two-tailed). Where p=.000, it is implied that p is <.0005 as per SPSS guidance (IBM, 2020b).

5I.3 Results

5I.3.1 Recruitment flow

Overall, 91 PwMSH were invited to participate in this study and 54 were enrolled. There were 62 adults without haemophilia who expressed interest in participating, and 33 were enrolled. Two participants in the CG did not return the BBAQ, and were therefore excluded from the analysis. A final sample size of 85 participants was included, which consisted of 54 participants in the HG, and 31 participants in the CG. Complete ActiGraph accelerometer data were obtained for 48 participants in the HG and 28 participants in the CG. Recruitment flow diagrams, including reasons for exclusion and non-participation, are provided in Figures 5I.1a and 5I.1b.

Figure 5l.1a: Recruitment flow chart (haemophilia group)

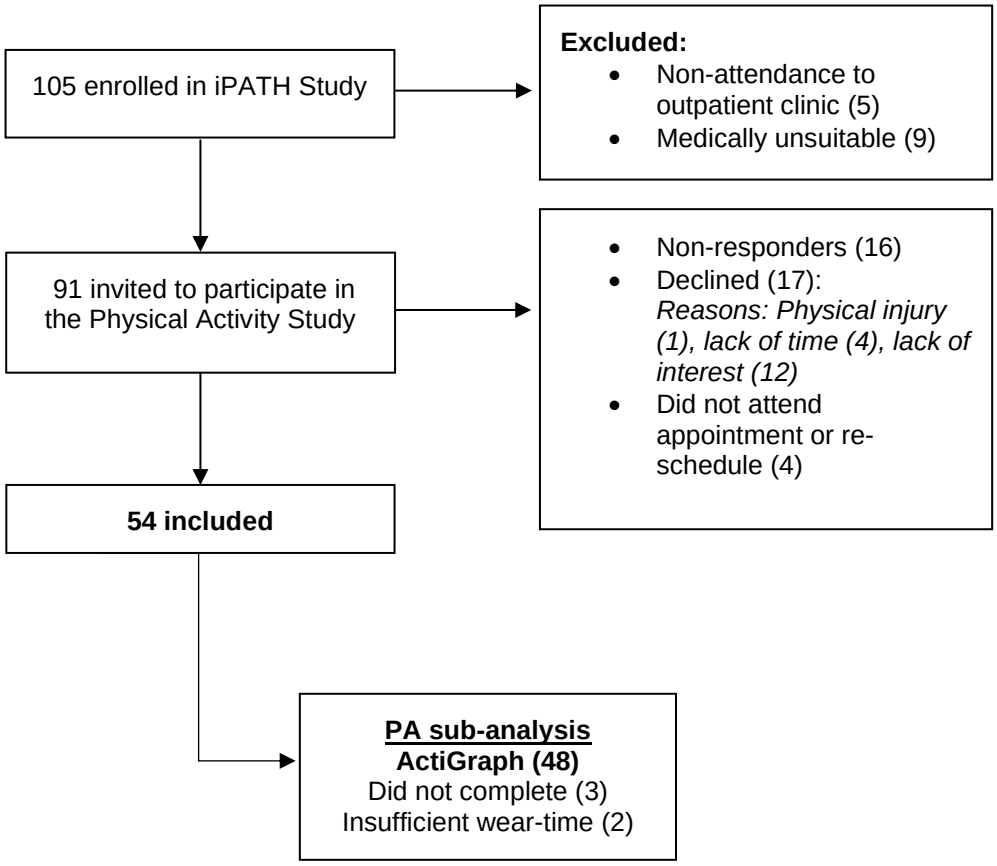
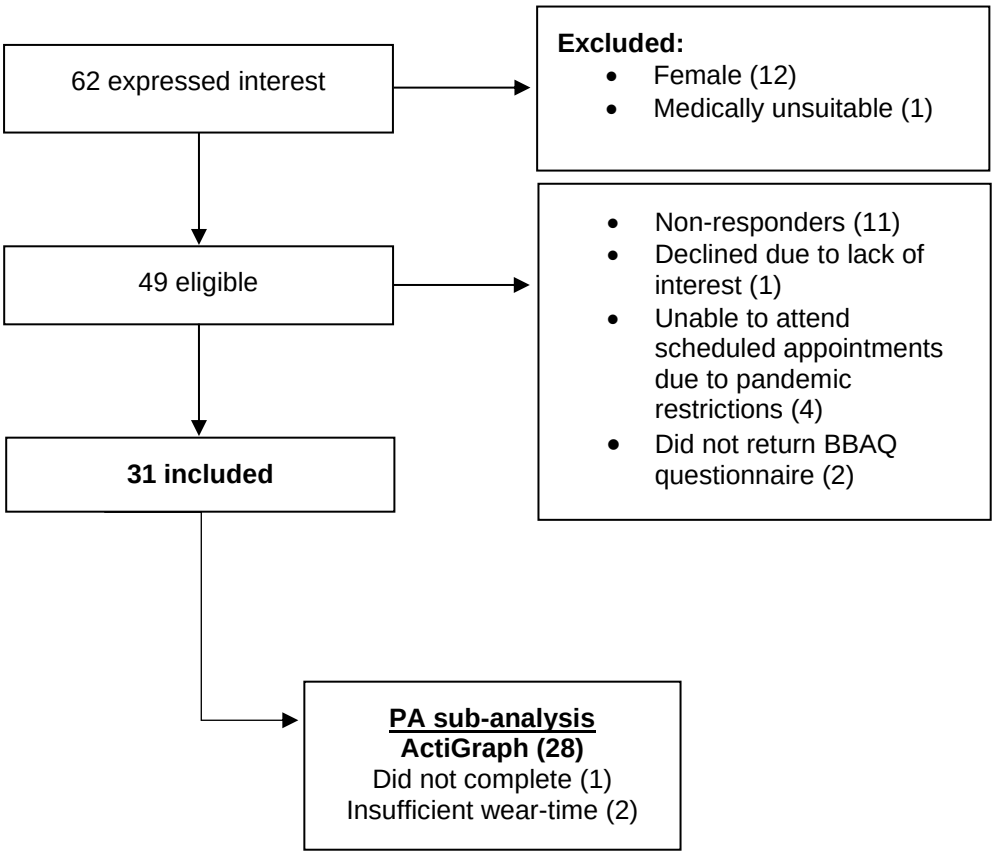


Figure 5I.1b: Recruitment flow chart (control group)



5I.3.2 Demographics and clinical phenotype

Demographic data are presented in Tables 5I.1a and 5I.1b. Severe haemophilia accounted for 87.0% of participants, and 13.0% had moderate haemophilia. A previous history of inhibitors was present in 13.0%. All participants with severe haemophilia and one participant with moderate HA were treated with prophylaxis (88.9%). Extended half-life factor replacement products were used by 89.6% of participants who were treated with prophylaxis. A previous history of HCV was present in 70.4%, and 26.0% were HIV positive. A previous surgical history of arthroplasty was present in 27.8%. Clinical phenotypic data regarding bleeding phenotype, joint health and the age at which prophylaxis was commenced are presented in Table 5I.1b. Demographic and clinical phenotypic data are presented according to group of haemophilia type and severity in Appendix XVIII. There were no significant differences between haemophilia type and severity for age [H(2)= 4.636; p= .098], height [H(2)= 1.109; p= .574], weight [H(2)= 1.136; p= .567], BMI [H(2)= .602; p= .740], WC [H(2)= .866; p= .649], WHtR [H(2)= 1.801; p= .406], or ABR [H(2)= .929; p= .628]. There were no significant differences between participants with HA or HB for the age at which prophylaxis was commenced [mean ranks: 19.26 vs. 26.50 (respectively); U= 253.5; p= .077] or the HJHS [mean ranks: 24.38 vs. 26.40 (respectively); U= 276.0; p= .648].

There were no significant differences between the HG and CG for age, height, weight or BMI. The HG had a significantly higher WC and WHtR compared to the CG. The HG were significantly less active than the CG in the total duration of time per week spent in MVPA and MVPA classified as Freedson bouts (≥10 minutes per bout). PA guidelines were met by 72.9% in the HG compared to 89.3% in the CG [$\chi 2(1) = 2.851$; p=.091; Fisher's Exact= .144; n= 76]. Guidelines achieved via Freedson bouts were met by 18.8% of the HG, compared to 57.1% in the CG [$\chi 2(1) = 11.809$; p=.001; Fisher's Exact= .001; n=76].

Table 5I.1a: Clinical demographics of participants with haemophilia

	Total (n)	Severe HA	Severe HB	Moderate HA	Moderate HB
	n (%)	n (%)	n (%)	n (%)	n (%)
n (%)	54 (100)	32 (59.3)	15 (27.8)	6 (11.1)	1 (1.8)
Inhibitor history					
History of inhibitors (non-active)	7 (13.0)	6 (85.7)	1 (14.3)	0	0
No history of inhibitors	47 (87.0)	26 (55.3)	14 (29.8)	6 (12.8)	1 (2.1)
Treatment regimen					
On demand	6 (11.1)	-	-	5 (83.3)	1 (16.7)
Prophylaxis	48 (88.9)	32 (66.7)	15 (31.2)	1 (2.1)	-
Treatment product					
Standard half-life product	3 (6.3)	3 (100)	0	-	-
Extended half-life product	43 (89.6)	27 (62.8)	15 (34.9)	1 (2.3)	-
Non-factor product	2 (4.1)	2 (100)	-	-	-
History of chronic infectious disease					
HCV (previous history)	38 (70.4)	19 (50.0)	14 (36.8)	5 (13.2)	0
HCV (no history)	16 (29.6)	13 (81.3)	1 (6.2)	1 (6.2)	1 (6.2)
HIV (positive)	14 (25.9)	11 (78.6)	1 (7.1)	2 (14.3)	0
HIV (negative)	40 (74.1)	21 (52.5)	14 (35.0)	4 (10.0)	1 (2.5)
Orthopaedic surgical history					
Ankle arthrodesis	7 (13.0)	3 (42.9)	4 (57.1)	0	0
Total knee replacement	6 (11.1)	4 (66.7)	2 (33.3)	0	0
Total elbow replacement	1 (1.9)	1 (100)	0	0	0
Total hip replacement	1 (1.9)	0	1 (100)	0	0

Values are presented as n (%); HA Haemophilia A **HB** Haemophilia B **HCV** Hepatitis C Virus **HIV** Human Immunodeficiency Virus

Table 5I.1b: Demographic, physical health and clinical phenotypic parameters

	HG (54)		CG (31)				
	Mean ± SD	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean ranks**	**U**	**p**
Age (years)	42 ± 13	44 (32, 51)	43 ± 9	42 (36, 46)	42.17 vs. 44.45	792.0	.681
Height (cm)	175.6 ± 7.1	174.2 (169.5, 181.7)	176.1 ± 6.9	175.9 (171.2, 180.8)	42.04 vs. 44.68	785.0	.635
Weight (kg)	83.8 ± 16.0	83.8 (72.5, 93.6)	81.0 ± 9.9	82.3 (73.6, 87.2)	44.58 vs. 40.24	922.5	.435
Body Mass Index (kg/m^2)	27.1 ± 4.6	27.0 (24.6, 30.1)	26.2 ± 3.4	25.2 (24.1, 28.3)	45.75 vs. 38.21	985.5	.175
Waist circumference (cm)†	93.2 ± 11.2	94.4 (85.6, 102.0)	87.2 ± 11.7	85.5 (78.1, 94.2)	47.78 vs. 33.47	1101.5	**.009***
Waist-height ratio†	.53 ± .07	.54 (.49, .57)	.50 ± .07	.48 (.45, .52)	47.61 vs. 33.76	1092.5	**.012***
Total MVPA (mins/wk)‡	230 ± 146	218 (139, 305)	341 ± 169	319 (232, 453)	32.53 vs. 48.73	385.5	**.002***
Freedson MVPA (mins/wk)‡	82 ± 96	46 (11, 124)	172 ± 98	177 (88, 248)	30.81 vs. 51.68	303.0	**.000***
ABR	3 ± 3	2 (1, 4)		-	-	-	-
HJHS¶	27 ± 13	28 (20, 34)		-	-	-	-
Age prophylaxis commenced (years)§	27 ± 19	26 (12, 48)		-	-	-	-

Values are presented as mean ± standard deviation and median (Q1, Q3); ABR Annualised Bleeding Rate **CG** Control Group **HG** Haemophilia Group **HJHS** Haemophilia Joint Health Score **mins/wk** Minutes per week **MVPA** Moderate-Vigorous Physical Activity **†** n= 53 (One participant did not complete physical assessment); **‡** n= 48 in HG and 28 in CG with complete ActiGraph data; Total MVPA= Total duration of time spent in MVPA; Freedson MVPA= Duration of time spent in MVPA bouts of ≥10 minutes; **§** n= 42 (Not applicable to 6 participants with moderate haemophilia and 6 participants with severe haemophilia did not answer)**;** ¶ n= 49 (No HJHS available for 5 participants with moderate haemophilia); **Values are compared using the Mann-Whitney U test; * statistically significant at α= .05 (two-tailed).**

5I.3.3 Barriers to physical activity

A score ≥5 for individual barrier domains is defined as a 'critical barrier' to PA by the BBAQ. Differences between critical barrier frequencies of the HG and CG are presented in Table 5I.2. Median scores of individual barrier domains according to subgroup comparisons are presented in Table 5I.3. Dunn's post hoc pairwise comparisons for significant Kruskal-Wallis test results are presented in Table 5I.4.

5I.3.3.1 Barriers by study group

The most common critical barriers to PA were lack of willpower, energy and time in both groups (Table 5I.2). Lack of skill was a significantly greater critical barrier to PA in the HG (Table 5I.2). Individual barrier domain scores were similar between the study groups, although social influence scores were notably higher in the HG, despite non-significant differences (Table 5I.3). Lack of skill was significantly higher in the HG (Table 5I.3). Individual barrier domains of the HG and CG are presented in Figure 5I.2.

5I.3.3.2 Barriers by type and severity of haemophilia

Lack of skill and resources were significantly different between groups (Table 5I.3). Lack of skill was a significantly greater barrier to PA in participants with moderate haemophilia compared to those with severe HB (Table 5I.4). This barrier was not significantly different between participants with moderate haemophilia and severe HA, or between participants with severe HA and severe HB. Lack of resources was a significantly greater barrier to PA in participants with moderate haemophilia compared to those with severe HB and severe HA (Table 5I.4). This barrier was not significantly different between participants with severe HA and severe HB. The remaining barrier domain scores were not significantly different between groups. Barrier domain scores are described by haemophilia type and severity in Figure 5I.3. Critical barriers to PA differed between groups; lack of willpower, energy and skill were deemed critical barriers to PA for participants with moderate haemophilia, but not for those with severe haemophilia.

5I.3.3.3 Barriers by HCV and HIV history

There were no significant differences in scores according to HCV history (Table 5I.3). Lack of skill was a significantly greater barrier to PA in participants who were HIV positive compared to participants who were HIV negative (Table 5I.3). There were no significant differences between participants according to HIV status for the remaining barrier domains. Barrier domain scores according to HCV history and HIV status are presented in Figures 5I.4 and 5I.5. Lack of willpower was a critical barrier to PA in participants without any history of HCV, whereas barrier scores did not reach this threshold in participants who had a previous history of HCV.

5I.3.3.4 Barriers by age

There were no significant differences between age groups of either study group for lack of time, social influence, lack of energy, lack of willpower and lack of resources (Table 5I.3). Fear of injury and lack of skill domain scores were significantly different between age and study groups (Table 5I.3). Adults <45 years in the HG reported fear of injury and lack of skill to be significantly greater barriers to PA than adults <45 years in the CG (Table 5I.4). Fear of injury and lack of skill were significantly greater barriers in adults ≥45 years in the HG compared to adults <45 years in the CG (Table 5I.4). Fear of injury was significantly greater in adults ≥45 years in the CG compared to adults <45 years in the CG (Table 5I.4). Lack of skill was a significantly greater barrier to PA for adults ≥45 years in the HG compared to adults <45 years in the HG (Table 5I.4). Barrier domain scores by age group (≥45 vs. <45 years) for both study groups are presented in Figures 5I.6 and 5I.7. Lack of willpower was a critical barrier to PA in adults <45 years old in the HG.

5I.3.3.5 Barriers by waist-height ratio

Lack of willpower, lack of skill and fear of injury were significantly different between WHtR groups (Table 5I.3). Lack of willpower, lack of skill and fear of injury were significantly greater barriers to PA in participants with increased WHtR in the HG compared to participants with normal WHtR in the CG (Table 5I.4). Lack of willpower was also significantly greater in adults with normal WHtR in the HG compared to participants with normal WHtR in the CG. Adults with increased WHtR in the CG had significantly greater barriers to PA due to lack of willpower and fear of injury compared to adults with normal WHtR in the CG (Table 5I.4). Lack of skill was a significantly greater barrier to PA in adults with increased WHtR in the HG compared to those with increased WHtR in the CG (Table 5I.4). There were no significant differences between groups for remaining barrier domain scores (Table 5I.3). Barrier domain scores are described according to WHtR classification (i.e. increased vs. normal) for both study groups in Figures 5I.8 and 5I.9. No critical barriers were identified according to WHtR classification in either group.

5I.3.3.6 Barriers by physical activity

Fear of injury and lack of skill domain scores were significantly different between groups according to total PA guideline achievement (i.e. at least ≥150-minutes of moderate intensity PA per week) (Table 5I.3). Lack of skill was a significantly greater barrier to PA in all participants in the HG, irrespective of guideline achievement, compared to participants who achieved guidelines in the CG (Table 5I.4). Fear of injury was a significantly greater barrier to PA for participants who did not achieve total PA guidelines in the HG and CG, compared to participants who did achieve guidelines in the CG (Table 5I.4). There were no significant differences between groups according to achievement of total guidelines or guidelines achieved via Freedson bouts for the remaining barrier domains (Table 5I.3). Barrier domain scores for both study groups according to PA guideline achievement are presented by PA guideline achievement in any duration of time in Figures 5I.10 and 5I.11. Lack of willpower was a critical barrier for participants who achieved PA guidelines in any

duration of time in the HG and for participants who did not achieve guidelines in the CG. Scores according to PA guideline achievement via Freedson bouts are presented in Figure 5I.12 and 5I.13.

Table 5I.2 Chi-square analysis of critical barriers to physical activity

	HG		CG				
	Yes	No	Yes	No			
	n (%)	n (%)	n (%)	n (%)	χ2	P	Fisher's exact
Lack of time†	13 (24.1)	41 (75.9)	5 (16.1)	26 (83.9)	.745	.388	.426
Social influence†	4 (7.4)	50 (92.6)	3 (9.7)	28 (90.3)	.134	.714	.702¶
Lack of energy‡	16 (30.2)	37 (69.8)	8 (25.8)	23 (74.2)	.184	.668	.804
Lack of willpower‡	24 (45.3)	29 (54.7)	8 (25.8)	23 (74.2)	3.146	.076	.104
Fear of injury§	3 (5.8)	49 (94.2)	1 (3.2)	30 (96.8)	.274	.601	1.000¶
Lack of skill‡	10 (18.9)	43 (81.1)	0	31 (100)	6.639	**.010***	**.011*¶**
Lack of resources‡	0	53 (100)	1 (3.2)	30 (96.8)	1.730	.188	.369¶

Descriptive values are presented as n (% of domain total); CG Control Group **HG** Haemophilia Group; **†** Lack of time, social influence n= 54 for HG and 31 for CG (full data)**; ‡** Lack of energy, willpower, skill and resources n= 53 for HG and 31 for CG (questions not fully completed by one participant in the HG)**; §** Fear of injury n= 52 for HG and 31 for CG (questions not fully completed by two participants in the HG); ¶ Expected cell count is less than 5; *** statistically significant at α= .05 (two-tailed).**

Table 5I.3: Comparison of barrier domains between groups and categories

	Lack of time†	Social influence†	Lack of energy‡	Lack of willpower‡	Fear of injury§	Lack of skill‡	Lack of resources‡
Total Group (n)							
HG (54)	3.0 (1.0, 4.3)	46.91; 2.0 (1.0, 3.3)¶	2.0 (0, 5.0)	4.0 (1.0, 6.0)	.5 (0, 2.0)	1.0 (0, 4.0)	1.0 (0, 2.0)
CG (31)	3.0 (0, 4.0)	36.19; 1.0 (0, 2.0)¶	3.0 (0, 5.0)	2.0 (0, 5.0)	0 (0, 1.0)	0 (0, 2.0)	1.0 (0, 3.0)
U	874.0	1048.0	768.0	975.5	964.0	1132.0	742.0
p	.732	.050	.614	.150	.099	**.002***	.436
Haemophilia type and severity (n)							
Moderate HA/HB (7)	4.0 (2.0, 5.0)	3.0 (2.0, 4.0)	5.0 (1.0, 5.0)	6.0 (5.0, 7.0)	3.0 (0, 7.0)	5.0 (1.0, 7.0)	3.0 (2.0, 3.0)
Severe HA (32)	3.0 (.3, 4.0)	2.5 (1.0, 3.0)	2.0 (0, 5.0)	4.0 (1.0, 6.0)	1.0 (0, 2.0)	1.0 (0, 4.0)	0 (0, 2.0)
Severe HB (15)	3.0 (0, 5.0)	2.0 (0, 4.0)	3.0 (1.0, 4.0)	2.0 (0, 4.0)	0 (0, 2.0)	1.0 (0, 2.0)	0 (0, 1.0)
H	1.742	1.805	1.881	5.659	2.593	7.079	7.883
p	.419	.405	.390	.059	.273	**.029***	**.019***
HCV history (n)							
Previous history (38)	3.0 (0, 4.0)	2.0 (1.0, 4.0)	2.0 (0, 5.0)	3.0 (1.0, 5.0)	.5 (0, 2.0)	2.0 (0, 4.5)	1.0 (0, 2.0)
No history (16)	3.0 (1.0, 5.8)	3.0 (1.0, 3.0)	1.5 (0, 5.8)	5.0 (1.5, 6.8)	.5 (0, 1.0)	1.0 (0, 3.0)	0 (0, 2.0)
U	359.5	308.0	283.0	369.0	254.0	264.0	277.5
p	.287	.939	.797	.154	.469	.525	.703
HIV status (n)							
Positive (14)	3.0 (0, 4.0)	2.5 (1.0, 4.3)	27.71; 2.0 (.8, 5.3)¶	4.0 (1.5, 5.3)	1.0 (0, 3.0)	34.64; 4.0 (.8, 5.3)¶	1.5 (0, 2.3)
Negative (40)	3.0 (1.0, 5.0)	2.0 (1.0, 3.0)	26.74; 3.0 (0, 5.0)¶	3.0 (1.0, 6.0)	0 (0, 2.0)	24.26; 1.0 (0, 3.0)¶	1.0 (0, 2.0)
U	259.5	312.0	283.0	279.0	307.0	380.0	313.5
P	.682	.520	.837	.903	.224	**.027***	.384
Age group (n)							
HG: ≥45 years (24)	2.0 (0, 3.0)	2.5 (1.0, 4.0)	2.0 (0, 4.0)	3.0 (1.0, 5.8)	1.0 (0, 3.0)	2.5 (.3, 5.0)	1.0 (0, 2.0)
<45 years (30)	3.0 (1.0, 5.0)	2.0 (1.0, 3.0)	3.0 (0, 5.5)	5.0 (1.0, 6.0)	0 (0, 2.0)	1.0 (0, 2.5)	0 (0, 2.0)
CG: ≥45 years (9)	4.0 (0, 4.0)	1.0 (0, 3.5)	4.0 (0, 5.5)	3.0 (0, 7.0)	1.0 (0, 4.0)	2.0 (0, 2.0)	1.0 (0, 3.0)
<45 years (22)	3.0 (0, 4.0)	1.0 (1.0, 2.0)	3.0 (1.0, 5.0)	1.5 (1.0, 4.0)	0 (0, 0)	0 (0, 1.0)	1.0 (0, 3.0)
H	3.278	4.429	.903	2.966	10.995	17.174	4.042
P	.351	.219	.825	.397	**.012***	**.001***	.257

Values are presented as median (Q1, Q3); Dichotomous variables were compared using the Mann-Whitney U Test, variables with >2 groups were compared using the Kruskal-Wallis H Test; CG Control Group **HA** Haemophilia A **HB** Haemophilia B **HCV** Hepatitis C Virus **HG** Haemophilia Group **HIV** Human Immunodeficiency Virus **MVPA** Moderate-Vigorous Physical Activity; **†** Lack of time, social influence n= 54 for HG and 31 for CG (full data)**; ‡** Lack of energy, willpower, skill and resources n= 53 for HG and 31 for CG (questions not fully completed by one participant in the HG)**; §** Fear of injury n= 52 for HG and 31 for CG (questions not fully completed by two participants in the HG); ¶ Values are reported as mean ranks and median (Q1, Q3) due to violation of similarly shaped data distribution assumption of the Mann-Whitney U Test; *** statistically significant at α= .05 (two-tailed).**

Table 5I.3 (continued)

		Lack of time†	Social influence†	Lack of energy‡	Lack of willpower‡	Fear of injury§	Lack of skill‡	Lack of resources‡
Waist-Height Ratio (n)								
HG:	**Increased (39)**	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	2.5 (0, 5.0)	3.5 (1.0, 6.3)	1.0 (0, 2.0)	2.0 (0, 5.0)	1.0 (0, 2.0)
	Normal (14)	3.0 (1.0, 5.0)	2.0 (1.0, 3.0)	2.0 (0, 5.3)	4.5 (2.5, 5.3)	0 (0, 2.0)	1.0 (0, 2.3)	0 (0, 2.0)
CG:	**Increased (11)**	4.0 (.3, 5.5)	1.0 (1.0, 2.8)	4.0 (.8, 6.0)	4.5 (1.5, 8.8)	1.0 (0, 3.5)	0 (0, 1.8)	1.0 (0, 3.0)
	Normal (19)	3.0 (0, 4.0)	1.0 (0, 2.0)	2.0 (0, 4.0)	1.0 (0, 3.0)	0 (0, 0)	0 (0, 2.0)	1.0 (0, 3.0)
	H	1.903	5.494	1.425	10.855	9.562	11.840	3.396
	p	.593	.139	.700	**.013***	**.023***	**.008***	.334
Achievement of total MVPA guidelines (n)								
HG:	**Yes (35)**	3.0 (1.0, 5.0)	3.0 (1.0, 3.0)	3.0 (0, 5.0)	5.0 (1.0, 6.3)	0 (0, 2.0)	1.5 (0, 4.0)	1.0 (0, 2.0)
	No (13)	3.0 (0, 4.0)	2.0 (1.5, 3.5)	2.0 (0, 4.5)	4.0 (1.5, 5.5)	1.0 (.5, 2.5)	1.0 (.5, 4.5)	1.0 (0, 2.0)
CG:	**Yes (25)**	3.0 (.5, 4.0)	1.0 (.5, 2.0)	3.0 (1.0, 5.0)	2.0 (1.0, 4.5)	0 (0, 1.0)	0 (0, 2.0)	1.0 (0, 3.0)
	No (3)	2.0 (0-6.0)	1.0 (1.0-6.0)	3.0 (0-6.0)	8.0 (0-9.0)	2.0 (1.0-4.0)	0 (0-1.0)	0 (0-6.0)
	H	1.383	5.447	1.122	3.141	10.941	8.101	1.119
	p	.710	.142	.772	.370	**.012***	**.044***	.773
Achievement of MVPA guidelines in Freedson bouts ≥10 minutes (n)								
HG:	**Yes (9)**	3.0 (1.0, 5.5)	3.0 (2.0, 4.0)	3.0 (0, 5.0)	4.0 (.8, 7.8)	.5 (0, 3.3)	2.5 (0, 5.0)	1.5 (.3, 2.8)
	No (39)	3.0 (1.0, 4.0)	2.0 (1.0, 3.0)	2.0 (0, 5.0)	4.0 (1.0, 6.0)	1.0 (0, 2.0)	1.0 (0, 3.0)	0 (0, 2.0)
CG:	**Yes (16)**	3.0 (0, 4.0)	1.0 (0, 2.0)	2.5 (.3, 4.8)	1.0 (.3, 4.8)	0 (0, .8)	0 (0, 2.0)	1.0 (0, 2.8)
	No (12)	4.0 (1.3, 5.5)	1.5 (1.0, 2.8)	4.0 (2.3, 5.8)	4.0 (1.3, 6.8)	.5 (0, 1.0)	0 (0, 1.0)	.5 (0, 3.0)
	H	2.047	7.390	1.677	3.142	2.700	7.790	2.832
	p	.563	.060	.642	.370	.440	.051	.418

Values are presented as median (Q1, Q3) or median (min-max range) if n<4; Dichotomous variables were compared using the Mann-Whitney U Test, variables with >2 groups were compared using the Kruskal-Wallis H Test; CG Control Group **HA** Haemophilia A **HB** Haemophilia B **HCV** Hepatitis C Virus **HG** Haemophilia Group **HIV** Human Immunodeficiency Virus **MVPA** Moderate-Vigorous Physical Activity; **†** Lack of time, social influence n= 54 for HG and 31 for CG (full data)**; ‡** Lack of energy, willpower, skill and resources n= 53 for HG and 31 for CG (questions not fully completed by one participant in the HG)**; §** Fear of injury n= 52 for HG and 31 for CG (questions not fully completed by two participants in the HG); ¶ Values are reported as mean ranks and median (Q1, Q3) due to violation of similarly shaped data distribution assumption of the Mann-Whitney U Test; *** statistically significant at α= .05 (two-tailed).**

Table 5I.4: Dunn's post hoc pairwise comparisons for significant Kruskal-Wallis H test results

	Lack of resources	Lack of willpower	Fear of injury	Lack of skill
	p	P	P	p
Haemophilia type and severity				
Moderate HA/HB vs. Severe HB	**.007***	**-**	**-**	**.008***
Moderate HA/HB vs. Severe HA	**.012***	**-**	**-**	.064
Severe HA vs. Severe HB	.550	**-**	**-**	.161
Age (<45 vs. ≥45 years)				
<45 (CG) vs. <45 (HG)	-	-	**.041***	**.028***
<45 (CG) vs. ≥45 (HG)	-	-	**.005***	**.000***
<45 (CG) vs. ≥45 (CG)	-	-	**.006***	.070
<45 (HG) vs. ≥45 (HG)	-	-	.367	**.029***
<45 (HG) vs. ≥45 (CG)	-	-	.187	.800
≥45 (HG) vs. ≥45 (CG)	-	-	.522	.196
Waist-height ratio (Normal vs. Increased)				
Normal (CG) vs. Increased (HG)	-	**.006***	**.004***	**.002***
Normal (CG) vs. Normal (HG)	-	**.026***	.133	.239
Normal (CG) vs. Increased (CG)	-	**.004***	**.016***	.828
Increased (HG) vs. Normal (HG)	-	.959	.364	.154
Increased (HG) vs. Increased (CG)	-	.362	.830	**.019***
Normal (HG) vs. Increased (CG)	-	.468	.365	.395
Total MVPA guidelines achieved (≥150 minutes/ week: Yes vs. No)				
No (CG) vs. Yes (CG)	-	-	**.020***	.591
No (CG) vs. Yes (HG)	-	-	.070	.138
No (CG) vs. No (HG)	-	-	.449	.090
Yes (CG) vs. Yes (HG)	-	-	.220	**.032***
Yes (CG) vs. No (HG)	-	-	**.006***	**.027***
Yes (HG) vs. No (HG)	-	-	.063	.554

CG Control Group **HG** Haemophilia Group **MVPA** Moderate-Vigorous Physical Activity**; * statistically significant at α= .05 (two-tailed)**.

Figure 5I.2: Barrier domains between the HG and CG

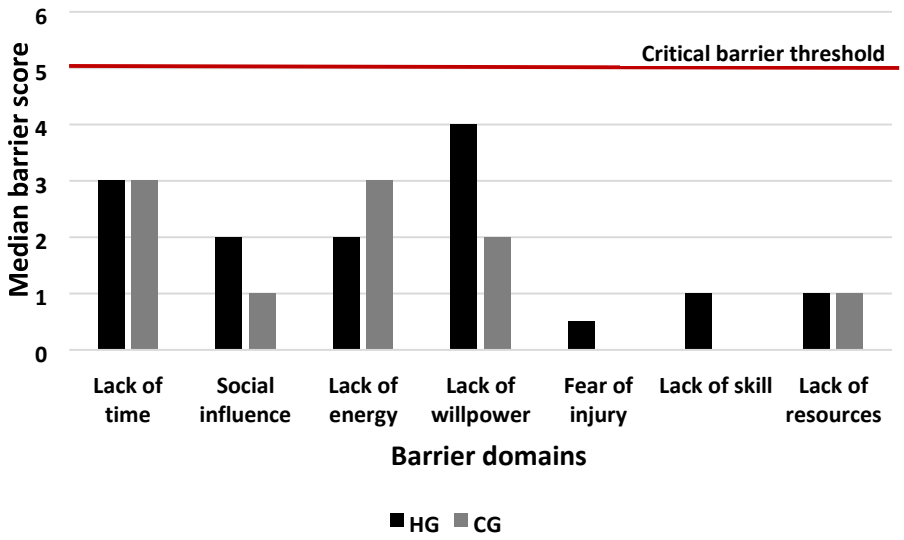


Figure 5I.3: Barrier domains by haemophilia type and severity

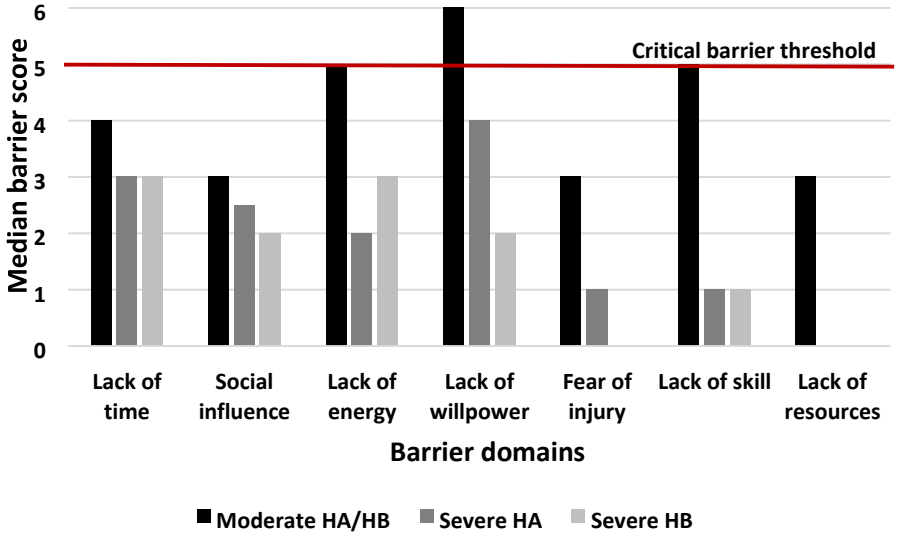


Figure 5I.4: Barrier domains by HCV history

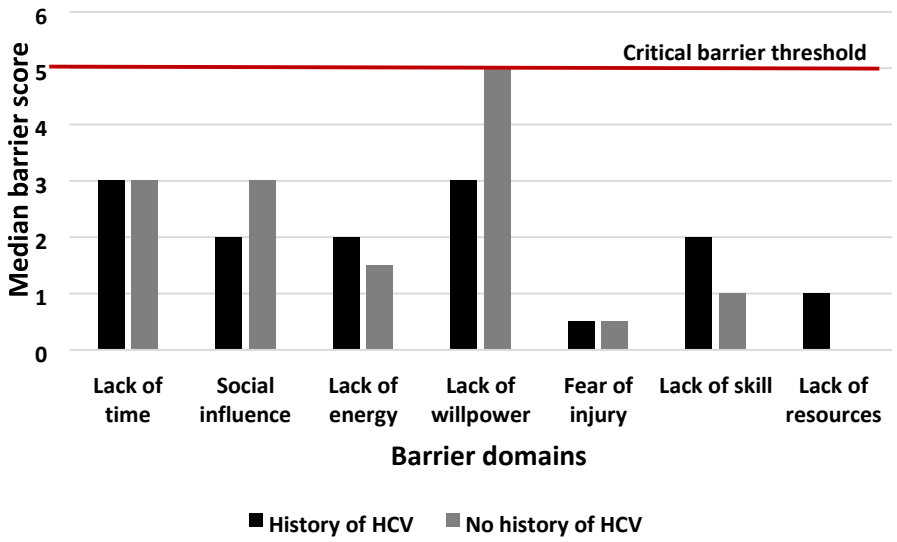


Figure 5I.5: Barrier domains by HIV status

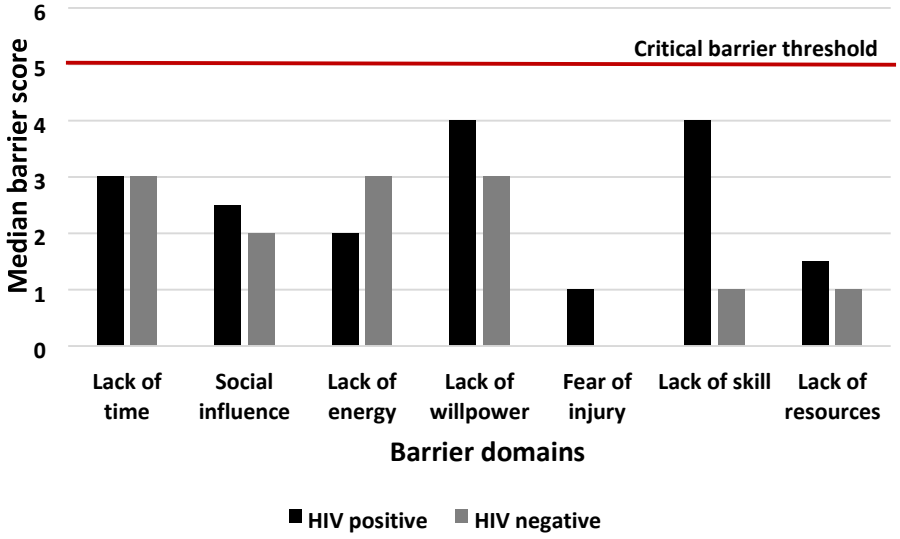


Figure 5I.6: Barrier domains by age group (HG)

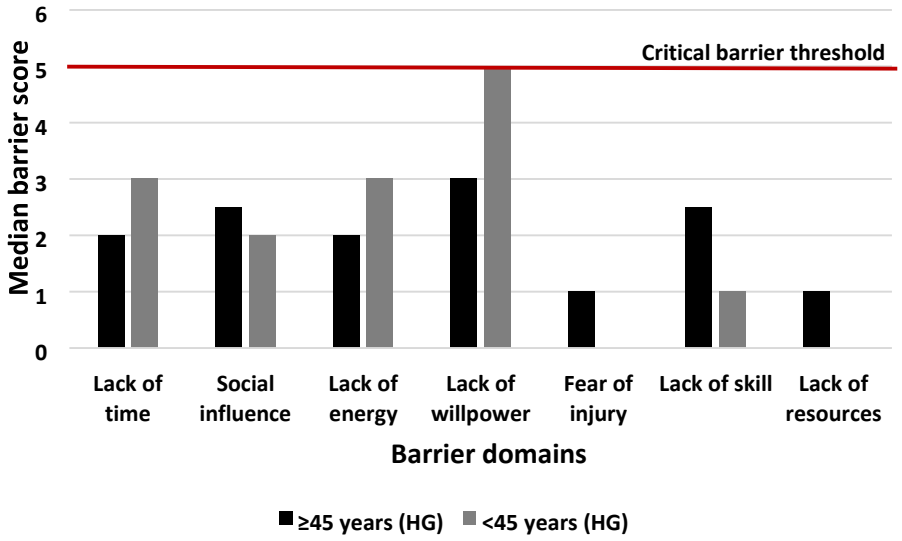


Figure 5I.7: Barrier domains by age group (CG)

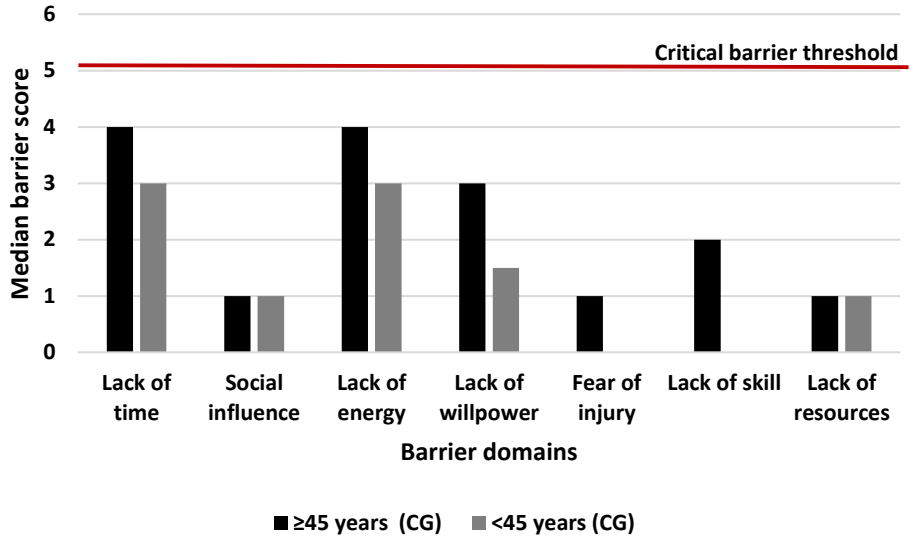


Figure 5I.8: Barrier domains by waist-height ratio group (HG)

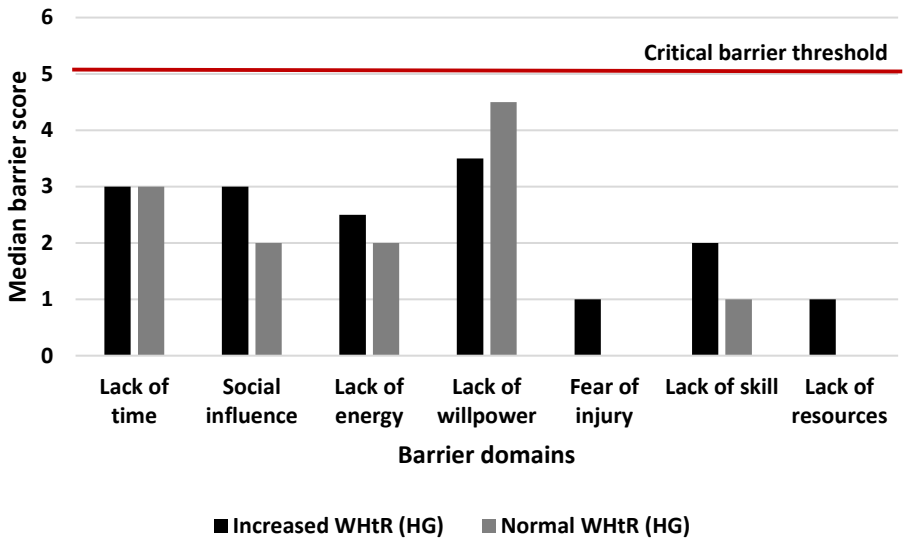


Figure 5I.9: Barrier domains by waist-height ratio group (CG)

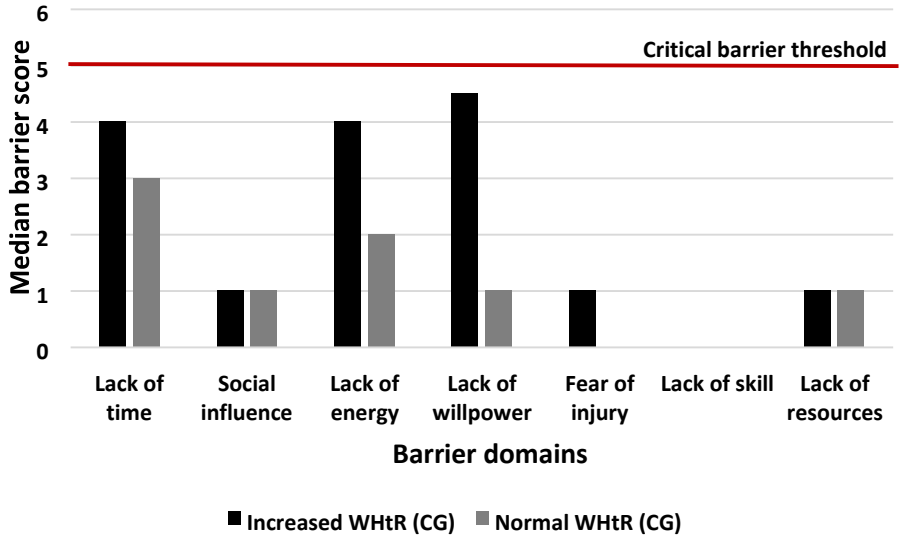


Figure 5I.10: Barrier domains by total PA guidelines (HG)

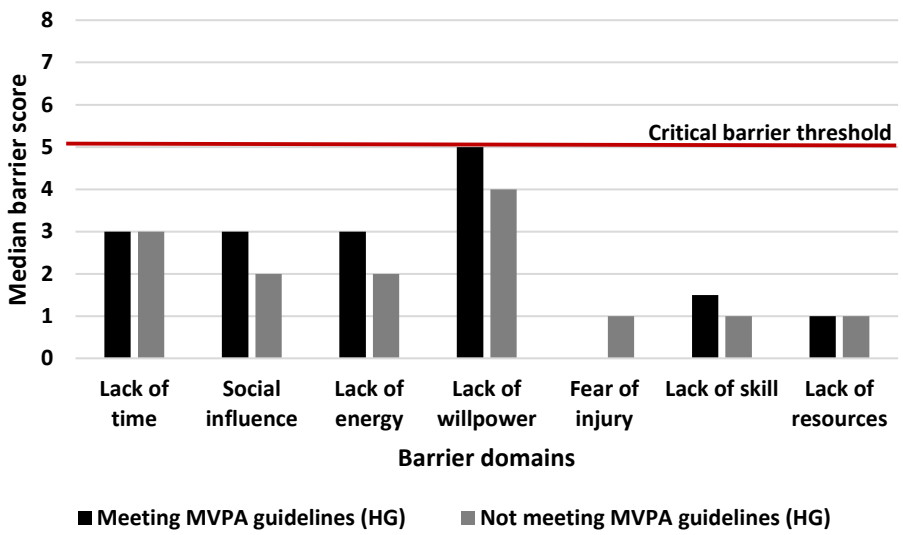


Figure 5I.11: Barrier domains by total PA guidelines (CG)

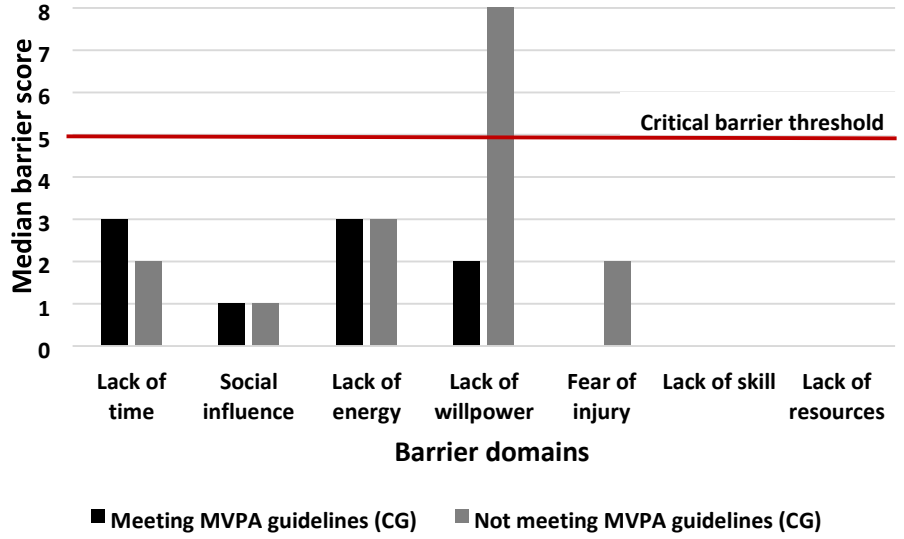


Figure 5I.12: Barrier domains by Freedson PA guidelines (HG)

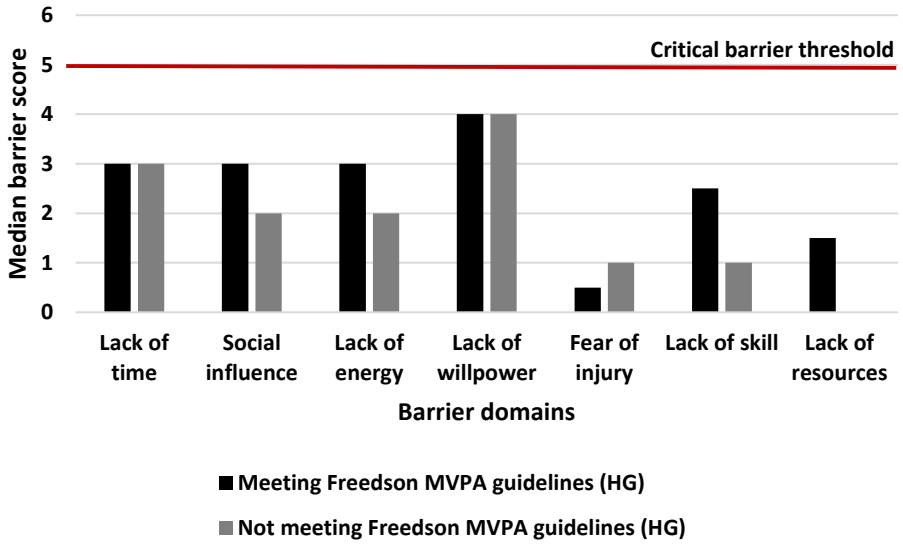
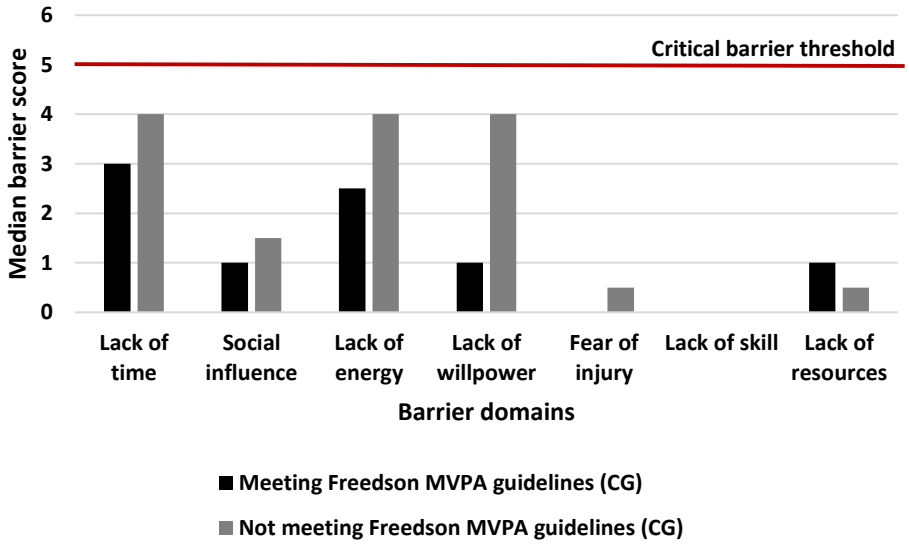


Figure 5I.13: Barrier domains by Freedson PA guidelines (CG)



5I.3.3.7 Clinical phenotype by critical barrier domain

Clinical phenotypic variables were compared by critical barrier domains. Results are presented in Table 5I.5. The ABR was significantly higher in participants who reported fear of injury to be a critical barrier to PA. The age at which prophylaxis was commenced was significantly lower in participants who reported a lack of energy or willpower to be critical barriers to PA. Clinical phenotypic variables were not significantly different according to the remaining critical barrier domains.

Table 5I.5: Comparison of clinical phenotypic parameters by critical barrier domains

	ABR				HJHS				Age prophylaxis commenced			
	n	**Mean ranks**	**U**	**p**	**n**	**Mean ranks**	**U**	**p**	**n**	**Mean ranks**	**U**	**p**
Lack of time	13 vs. 41	21.04 vs. 29.55	182.5	.085	12 vs. 37	21.33 vs. 26.19	178.0	.306	12 vs. 30	17.67 vs. 23.03	134.0	.208
Social influence	4 vs. 50	21.13 vs. 28.01	74.5	.414	4 vs. 45	37.13 vs. 23.92	138.5	.076	3 vs. 39	22.00 vs. 21.46	60.0	.963
Lack of energy	16 vs. 37	25.94 vs. 27.46	279.0	.739	13 vs. 35	21.15 vs. 25.74	184.0	.312	11 vs. 30	13.68 vs. 23.68	84.5	**.016***
Lack of willpower	24 vs. 29	28.15 vs. 26.05	375.5	.618	20 vs. 28	22.20 vs. 26.14	234.0	.335	16 vs. 25	14.06 vs. 25.44	89.0	**.002***
Fear of injury	3 vs. 49	43.17 vs. 25.48	123.5	**.047***	1 vs. 47	10.00 vs. 24.81	9.0	.417	**(insufficient data)**			
Lack of skill	10 vs. 43	29.70 vs. 26.37	242.0	.534	6 vs. 42	31.33 vs. 23.52	167.0	.213	4 vs. 37	31.13 vs. 19.91	114.5	.075

Variables were analysed using the Mann-Whitney U test, n and mean ranks are presented in order of yes vs. no frequencies for each critical barrier domain; Lack of resources not compared by clinical phenotype as n= 0 for this domain; Age prophylaxis not compared by fear of injury domain due to missing data; ABR Annualised Bleed Rate **HJHS** Haemophilia Joint Health Score**; * statistically significant at α= .05 (two-tailed).**

5I.4 Discussion

This study aimed to compare barriers to PA between adult PwMSH and adults without haemophilia, as well as to determine the relationship between barriers to PA and age, body composition, PA levels and clinical phenotype. Lack of willpower, energy and time were the most common barriers to PA in both PwMSH and adults without haemophilia, whilst lack of resources, fear of injury, lack of skill and social influences were less common barriers across both study groups. There were no significant differences between study groups for individual barrier domain scores, except for the domain "lack of skill", which was significantly higher in PwMSH. Type and severity of haemophilia, age, body composition and PA were associated with a variety of barrier domains. This study also found that the majority of barriers were not significantly related to HCV or HIV status.

5I.4.1 Lack of willpower, energy and time

The present analysis offers insights into a variety of barriers to PA in adult PwMSH, which are also experienced by adults without haemophilia from the general population. Domain scores were statistically comparable between the HG and CG for the vast majority of barriers, including the most prevalent barriers in both groups which were lack of willpower, lack of energy and lack of time. These barriers should be given consideration when designing interventions to address the issue of physical inactivity in the adult haemophilia population. The fact that barriers were not significantly different between PwMSH and the general population highlights that interventions that aim to address physical inactivity in adults with haemophilia should address both general and haemophilia-specific barriers to PA.

Statements 4, 11 and 18 of the BBAQ (Appendix XV) relate to initiating and adhering to PA or exercise, and contribute to the lack of willpower domain score. Lack of willpower scores were significantly higher in adults with an increased WHtR in both the HG and CG compared to adults with normal WHtR in the CG. This is not surprising as lack of motivation has been identified as a barrier to PA in obese adults (Burgess et al., 2017). However, participants with normal WHtR in the HG also scored significantly higher for lack of willpower compared to participants with normal WHtR in the CG, and lack of willpower was not significantly related to age or PA engagement. It therefore may be that PwMSH encounter more challenges in self-motivation and willpower to engage in PA compared to the general population. Interestingly, the age at which prophylaxis was commenced was also significantly lower in PwMSH who reported that lack of willpower and energy were critical barriers to PA. This may suggest that prophylactic treatment regimens could be related to increased fatigue, or other internal factors impacting on PA engagement and behaviour in younger PwMSH. This may be affected by the number of years of ongoing treatment. Internal personal barriers to PA, as well as the potential influences of fatigue and treatment burden on PA in PwMSH, therefore warrant further investigation.

5I.4.2 Lack of skill

Lack of skill was a significantly greater barrier to PA in PwMSH compared to adults without haemophilia. Statements 6, 13 and 20 of the BBAQ (Appendix XV) contribute to the barrier domain score for lack of skill. These statements address concerns of not learning how to play sport at a younger age, difficulties in learning a new sport at an older age, and not being 'good enough' at PA to make it enjoyable. All participants in the HG, irrespective of PA guideline achievement, had significantly higher lack of skill scores than adults who achieved PA guidelines in the CG. Participants with increased WHtR in the HG also had significantly higher scores compared to all participants in the CG, irrespective of their WHtR status. Lack of skill was also a significantly greater barrier for all participants in the HG irrespective of age when compared to younger participants in the CG, although older adults in the HG reported this to be a greater barrier to PA than younger adults in the HG. Furthermore, participants who were HIV positive demonstrated significantly higher lack of skill scores than participants who were HIV negative. These findings are therefore suggestive that lack of skill is a prominent barrier to PA in adults with haemophilia, which may indicate a lower variety of PA options that they can safely and confidently engage in. This barrier may also be more enhanced in older PwMSH, and those who have an increased WHtR and comorbid HIV.

Study I of this thesis which examined PA in adult PwMSH, provided qualitative information from a small number of participants who reported that they weren't allowed to engage in PA during childhood due to a fear of bleeds and joint damage. A lack of opportunity to learn how to play sport and engage in PA and exercise during childhood, may explain this pertinent barrier to PA in adult PwMSH, particularly amongst the older generations who did not grow up with optimal treatment options. Participants with moderate haemophilia also reported higher lack of skill scores than adults with severe haemophilia, which may indicate that opportunities to learn PA skills earlier in life were further limited by a lack of prophylactic treatment, although this interpretation is limited by the small sample size of the moderate haemophilia group. This finding emphasises the importance of advising PwMSH to engage in types of exercise and PA that they are capable of achieving and enjoying, which is also important for maintaining adherence to long-term PA engagement (Sörensen, 2005, Williams et al., 2006). This population may benefit from individualised training, supervision and support from qualified exercise professionals when initiating a new exercise or PA programme, in order to improve their confidence and skills when undertaking PA.

5I.4.3 Social influences

Although it was not a critical barrier to PA for the majority of participants in both study groups, social influence scores were notably higher in the HG compared to the CG, and results approached statistical significance. A small number of previous studies have also reported social barriers to PA in adult and adolescent people with haemophilia (Buxbaum et al., 2010, Flaherty et al., 2018). Statements 2, 9 and 16 of the BBAQ (Appendix XV) contribute to the social influence domain score and relate to the influences of PA behaviour amongst family and friends, embarrassment of how one looks when they exercise and opportunities to engage in PA when socialising with family and friends.

These findings suggest that influences from family and peers may impact PA behaviour in PwMSH more than the general population. Families with a history of haemophilia may be inclined to have a more protective attitude to PA. Non-affected family members may have witnessed physical health complications associated with haemophilia throughout generations of affected family members, and this may lead to discouragement of PA out of fear that PA may be harmful or unsafe. It may therefore be important to involve and educate family members and significant others when designing PA programmes for their affected family member, although further exploration of PA perceptions amongst partners, families and friends of people with haemophilia is needed.

5I.4.4 Fear of injury

As might be expected, fear of injury was a more pertinent barrier to PA in the HG compared to the CG, although notably scores were overall low for this domain. Despite low scores, PwMSH in both older and younger age groups had significantly higher fear of injury scores compared to younger participants in the CG. Certainly, older participants in the CG also had significantly higher fear of injury scores than younger participants in the CG, as this is consistent with an established increase in fear of harm caused by PA in older adults (Franco et al., 2015). It is interesting to note that this barrier was also greater in younger adults with haemophilia, as well as the association between lower engagement in PA, increased WHtR and fear of injury. Fear of injury, leading to decreased participation in PA may therefore have a negative impact on body composition.

Furthermore, despite the limited sample size, ABR was significantly higher in participants who reported that fear of injury was a critical barrier to PA. The safety of exercise, fear of bleeds and pain have been qualitatively reported to present barriers to engaging in PA and exercise rehabilitation in a small number of previous studies (Mulvany et al., 2010, Flaherty et al., 2018, McLaughlin et al., 2021). This is understandable considering the relationship between bleeds and the safety of different volumes and types of PA is unclear (Strike et al., 2016, Kennedy et al., 2021). This may lead to a lack of confidence, increased fear and confusion as to the safety of exercise, despite the fact that PA is encouraged amongst the general haemophilia population because of its numerous associated health benefits (Anderson and Forsyth, 2017, Srivastava et al., 2020). People with haemophilia are also encouraged to consult with their musculoskeletal healthcare specialist prior to engaging in certain PA and sports. This finding again highlights the need for adequate patient education, support and individualised management to reduce the fear of injury in PwMSH. It should be noted that the BBAQ is not specific to haemophilia-related injuries such as bleeds and joint damage, therefore the fear of injury domain may have been underestimated in the present sample. Furthermore, other aspects of barriers to PA in PwMSH may have been omitted. A validated tool to assess barriers to PA in people with haemophilia does not currently exist, but would be useful in order to ascertain both general and haemophilia-specific barriers to PA in this population.

5I.4.5 Limitations

A number of additional limitations of this analysis, other than those already discussed, warrant consideration. The small sample size may have increased the risk of a type II error in statistical analyses. This is a common limitation of many studies in haemophilia research considering it is a rare genetic disorder. Furthermore, the convenience sampling methods used may have contributed to a less representative sample of both target populations. Non-response bias could not be measured as the demographics and characteristics of non-responders were not obtainable. The BBAQ and a number of disease-related measures were self-reported in nature, which may have introduced some degree of recall or response bias. Lastly, causation or temporality cannot be inferred between the variables analysed in relation to each other due to the cross-sectional nature of the study design, however the study findings offer numerous insights which may be explored in further detail in future appropriately designed studies.

5I.5 Conclusion

This study revealed that a variety of barriers to PA affect adult PwMSH. Lack of willpower, time and energy were the most prominent barriers to PA for both PwMSH and adults without haemophilia, although social influences and fear of injury were also reported by PwMSH. Lack of skill was a more significant barrier to PA in PwMSH compared to adults without haemophilia, especially in older adults who may have had less access to treatment as children. Age, PA, body composition, severity of haemophilia, bleeding rate and the age at which prophylaxis was commenced were all associated with various barriers to PA, and these findings warrant further examination in future studies. Qualitative studies may provide additional useful information when designing effective interventions to help PwMSH overcome common barriers to PA. A validated tool to assess barriers to PA specifically in the haemophilia population is also needed, and warrants investigation in future research.

Section II: Study IIIb: An investigation of pain and functional disability in adults with moderate and severe haemophilia

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5II.1 Introduction

PwMSH may experience traumatic or spontaneous bleeding into joints, resulting in significant pain, swelling and reduced function (Mannucci and Tuddenham, 2001). In the longer term, repeated haemarthroses may result in synovitis and osteochondral destruction causing chronic haemophilic arthropathy, which characteristically affects the elbows, knees and ankles (Raffini and Manno, 2007). For PwMSH, significant phenotypic variability exists, resulting in differing rates and severity of bleed frequency, haemophilic arthropathy and functional disability (Franchini and Mannucci, 2017). PwMSH with a severe bleeding phenotype are typically treated with regular intravenous administration of recombinant clotting factor concentrates, which aims to prevent bleeding and subsequent haemophilic arthropathy. Treatment regimens are classified as primary, secondary or tertiary prophylaxis. Primary prophylaxis is commenced before the second clinically evident joint bleed, and before three years of age (Srivastava et al., 2020). Secondary prophylaxis is commenced after two or more joint bleeds, before the onset of evident haemophilic arthropathy. Tertiary prophylaxis is commenced in adulthood, after the onset of clinically evident haemophilic arthropathy.

With wider use of prophylaxis, novel replacement therapies and gene therapy, bleed rates have markedly decreased in recent decades (Mancuso et al., 2021). However, for adults on secondary and tertiary prophylaxis, the burden of pre-existing haemophilic arthropathy and pain may continue to impact physical and social functioning. Difficulties with activities of daily living (ADLs) due to pain have been described in PwMSH, and increased age and intensity of pain have been identified as predictors of functional disability (Wallny et al., 2001, Santavirta et al., 2001, van Genderen et al., 2006). Functional disability contributes to lower levels of PA and pain presents a barrier to exercising for some (Flaherty et al., 2018), further perpetuating disability. Furthermore, chronic pain in the general population has been associated with elevated cardiometabolic risk factors, including obesity (Goodson et al., 2013), which should also be considered in PwMSH who may be less physically active and potentially more prone to cardiometabolic risk factors.

The previous section of this chapter examined barriers to PA using the Barriers to Being Active Quiz; however, the domains of pain and functional disability were not examined by this questionnaire. This study therefore aimed to determine the prevalence of pain and functional disability amongst adult PwMSH. Age, PA levels, body composition and clinical phenotypic parameters were also examined

in relation to pain and functional disability, providing a comprehensive analysis of the complications resulting from haemophilic arthropathy.

5II.1.1 Aim

The primary aim of this study is to examine pain and functional disability in adult PwMSH. The secondary aim is to examine the relationship between pain and functional disability with age, PA levels, body composition and clinical phenotypic parameters.

5II.1.2 Objectives

5II.1.2.1 Primary objective

1) To determine the prevalence of pain and functional disability in adult PwMSH.

5II.1.2.2 Secondary objectives

1) To determine the relationship between pain and functional disability with age.

2) To determine the relationship between pain and functional disability with PA levels.

3) To determine the relationship between pain and functional disability with body composition.

4) To determine the relationship between pain and functional disability with clinical phenotype.

5II.2 Methodology

5II.2.1 Study design, setting and participants **(See sections 2.2-2.5)**

Recruitment and data collection for this cross-sectional study took place between April 2018 and March 2020 at the National Coagulation Centre, St. James's Hospital Dublin. Patients were approached during routine clinical visits and were provided with an information leaflet inviting them to voluntarily participate (Appendix VIII). Eligibility criteria included males ≥18 years with diagnosed moderate (1-5%) or severe (<1%) Factor VIII or Factor IX deficiency (Haemophilia A and B, respectively), without active inhibitors. Individuals who lacked capacity to provide informed consent, those with acute medical concerns, recent bleeds or who were non-ambulatory were not eligible. This study received ethical approval from St. James's Hospital/ Tallaght University Hospital Joint Research Ethics Committee (Appendix IV), and informed, written consent was obtained from all study participants (Appendix IX).

5II.2.2 Demographics and outcome measures

5II.2.2.1 Demographic information

Age, type and severity of haemophilia, treatment regimen, prescribed analgesia within the previous year (where available), the age at which prophylaxis was commenced and inhibitor history were recorded.

5II.2.2.2 Outcome measures

The following outcome measures were assessed to fulfil the aims and objectives of this study:

- Bleeding phenotype was examined by calculating the ***Annualised Bleeding Rate (ABR)*** for each participant with haemophilia (See section 2.6.2.1).
- Joint health was examined using the participants' most recent ***Haemophilia Joint Health Score (HJHS; version 2.1)*** (See section 2.6.2.2).
- Anthropometry and body composition were measured using ***height, weight, Body Mass Index (BMI), waist circumference (WC) and waist-height ratio (WHtR)*** (See section 2.6.5.1).
- PA was objectively measured over one week using the ***ActiGraph GT3X-BT accelerometer***, and raw data were analysed using the ActiLife software (See section 2.6.3.1).
- A validated tool for assessing patient reported outcomes in people with haemophilia, ***the Patient Reported Outcomes Burdens and Experiences (PROBE) questionnaire (See section 2.6.61, Appendix XIV)***, was used to examine pain, difficulties with ADLs and their impact on activities and quality of life. It assesses the prevalence, causes and impact of acute and chronic pain, analgesia, difficulties with ADLs and the presence of target joints. The PROBE defines acute pain as "…pain that arises in response to an event (like an injury or bleeding episode)"; and chronic pain as "…pain from a persistent cause…" which "…can vary in frequency and intensity (like back pain, pain from sore joints, or arthropathy)", over the previous twelve months. Target joints were clinically defined as three or more consecutive, spontaneous bleeds into a single joint within the previous six months (Blanchette et al., 2014). The PROBE includes questions on self-perceived target joints (without formal definition), as well as a separate question on the presence of three or more consecutive, spontaneous bleeds into any one joint in the previous six months (i.e. the clinical definition of a target joint).

5II.2.3 Statistical methods

Data were analysed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data distributions were assessed using the Shapiro-Wilk test and visual inspection of histograms, normal Q-Q plots, and box and whisker plots. Continuous data are presented as mean ± standard deviation and median and interquartile range

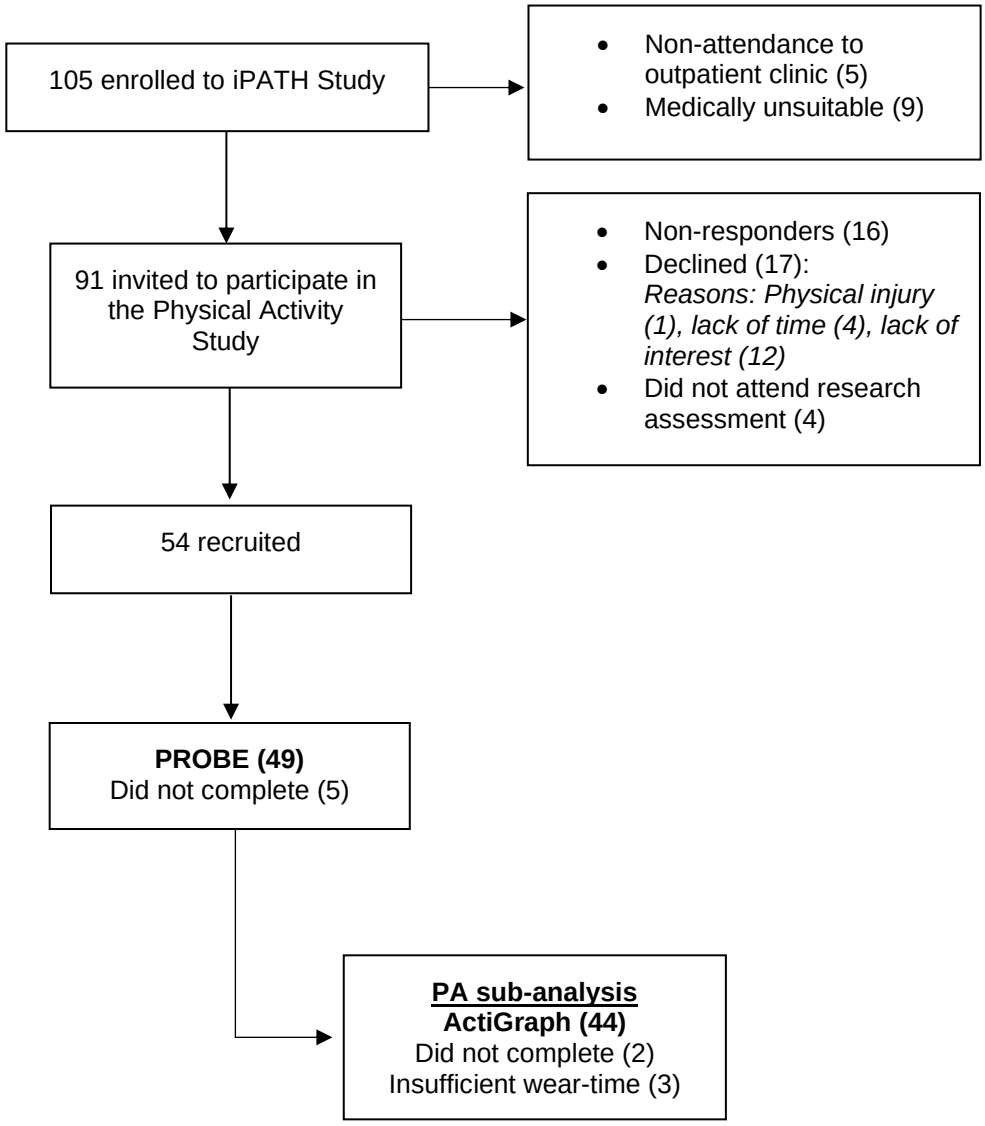
(IQR; Q1, Q3), as appropriate. Categorical data are presented as frequency counts and percentages, and were also separated by age groups (18-32 vs. 33-52 vs. 53-71 years). Chi-square tests were used to examine relationships between categorical data. Fisher's exact test was used when the expected cell count of one or more cells was less than five. Due to the small sample size and non-parametric distribution of continuous data, non-parametric statistical tests were chosen. Between-group differences were assessed using the Mann-Whitney U test for dichotomous variables. The shape of data distribution between groups was dissimilar for the majority of statistical comparisons, thus mean rank values are additionally reported. The Kruskal-Wallis H test was used to compare variables between more than two groups. Dunn's post hoc pairwise comparisons were generated for statistically significant results of the Kruskal- Wallis H test. The following parameters were compared by categories of acute and chronic pain in the previous 12 months, current difficulties with ADLs and target joint prevalence: age; ABR; age at which prophylaxis was commenced; HJHS; BMI; WC; WHtR; and PA. Spearman's rank-order correlations via coded dichotomous variables were used to explore the relationship between pain and functional disability and continuous variables. Missing data were excluded from analyses and are highlighted throughout the text, tables and figures as appropriate with accompanying explanations. Significance was taken at alpha (α)= .05 (two-tailed). Where p=.000, it is implied that p is <.0005 as per SPSS guidance (IBM, 2020b).

5II.3 Results

5II.3.1 Recruitment flow

The PROBE was completed by 49 participants, and data on prescribed analgesia were available for 29 participants. A high level of compliance with the ActiGraph accelerometer was achieved by 44 participants. Recruitment flow and reasons for participation exclusion or non-inclusion in the analysis are presented in Figure 5II.1.

Figure 5II.1: Recruitment flow chart



5II.3.2 Demographics and clinical phenotype

Descriptive statistics for demographic variables are presented in Table 5II.1. The median age of the sample was 44, and ranged from 18-71 years. A total of 61% participants had severe HA, 27% had severe HB, and the remaining participants had moderate haemophilia. Those with severe haemophilia were treated with regular prophylaxis, whilst those with moderate haemophilia were treated on demand. The median ABR was 2 (IQR: 1, 4), and no participant had a clinically diagnosed target joint. The median age at which prophylaxis was commenced was 26 (13, 49) years. A small proportion (12%) had a past history of inhibitors, but these were inactive during the study period. History of significant haemophilic arthropathy was evident with a median HJHS of 28 (20, 36). Haemophilic arthropathy was significantly influenced by age [H(2)= 12.731; p= .002]. Post hoc pairwise comparisons revealed adults in the youngest age group had a significantly lower HJHS than adults in the middle-aged (p= .044) and oldest age group (p= .000). Adults in the oldest group also had a significantly higher HJHS than the middle-aged group (p= .030). The ankles were most severely affected, followed by the elbows and knees. There were no significant differences by type of haemophilia for age (mean rank: HA 23.24, HB 29.39; U= 306.5, p= .173), ABR (mean rank: HA 25.74, HB 23.14; U= 219.0, p= .559), the age at which prophylaxis was commenced (mean rank: HA 17.69, HB 23.42; U= 203.0, p= .140) or HJHS (mean rank: HA 22.45, HB 22.62; U= 203.0, p= .969).

Participants spent a median duration of 1882 (1495, 2399) minutes/week in light PA, 213 (104, 308) minutes/week in total MVPA and 41 (11, 97) minutes/week in MVPA sustained in bouts ≥10 minutes (i.e. Freedson bouts). Guideline recommended levels of PA were achieved by 70%, however only 20% achieved this via Freedson bouts. The majority of the group (67%) were overweight or obese as per the World Health Organisation cut-off values for BMI (WHO, 2021). Furthermore, 54% had an increased WC above the normative cut-off for men (>94cm), and 75% had an increased WHtR above the normative standard (>.50). There were no significant differences by type of haemophilia for light PA (mean rank: HA 22.23, HB 23.07; U= 218.0, p= .840), total MVPA (mean rank: HA 22.27, HB 23.00; U= 217.0, p= .860), Freedson MVPA (mean rank: HA 22.13, HB 23.29; U= 221.0, p= .781), BMI (mean rank: HA 24.76, HB 25.61; U= 253.5, p= .851), WC (mean rank: HA 23.46, HB 27.04; U= 273.5, p= .421) or WHtR (mean rank: HA 23.35, HB 27.29; U= 277.0, p= .375).

5II.3.3 Pain and functional disability

5II.3.3.1 Pain

The prevalence of acute pain, chronic pain and analgesic requirements by age groups are presented in Table 5II.2. Both acute (72%) and chronic (71%) pain were prevalent. There was no significant association between age and acute pain, but participants in the youngest age group reported significantly less chronic pain compared to the middle-aged group (p= .011) and the oldest age group (p= .041). Reports of pain were not significantly different between the middle and oldest age groups (p= 1.000). The use of pharmacological analgesia was high (92%) and similar across age groups.

Pharmacological analgesia was reportedly taken less frequently, according to percentage of time, by younger adults compared to older adults (p= .114; Figure 5II.2).

Details of prescribed pharmacological analgesia were available for 29 participants [Age: 45 (35, 55) years; BMI: 28.3 (25.4, 31.1) kg/m^2; HJHS: 31 (21, 36)]. More than one pain medication was prescribed in 45%. COX-2 inhibitors (e.g. Etoricoxib) were the most commonly prescribed medications (79%), followed by paracetamol (38%) and weak opioid analgesics (38%). Age-related associations with analgesia were not statistically significant.

Causes and impact of acute and chronic pain are presented in Table 5II.3. Participants reported various causes of acute and chronic pain, with common causes of both reported to be walking, stair climbing, exercising or playing sport amongst others. Pain also interfered with quality of life and a number of activities including general activity levels, exercise or playing sport, mobility, mood, sleep and overall enjoyment of life.

Results of variables compared by categories of acute and chronic pain are presented in Table 5II.4. Differences between individuals who reported acute pain compared to those who did not were not significant for age, clinical phenotypic or body composition variables. Correlations between acute pain and all variables were weak (Table 5II.5). Those who experienced chronic pain demonstrated no significant differences to those who did not in body composition or the HJHS, however they were significantly older, had a significantly higher ABR and commenced prophylaxis at a significantly older age (all p<.05). Chronic pain was moderately correlated with ABR and the age at which prophylaxis was commenced, and all remaining correlations were weak (Table 5II.5).

ActiGraph data were available for 44 participants [Age: 45 (33, 55) years; BMI: 27.4 (24.8, 30.4) kg/m^2; HJHS: 27 (21, 34)]. Those who experienced acute pain demonstrated no significant differences to those who did not for time spent in light PA. Participants who reported acute pain spent less time in total MVPA and Freedson MVPA compared to participants without acute pain, although differences were not significant. Those who experienced chronic pain also demonstrated no significant differences to those who did not for light PA, total MVPA or Freedson MVPA.

5II.3.3.2 Functional disability

The prevalence of functional difficulties by age groups are presented in Table 5II.2, and results of variables compared by category of functional difficulty are presented in Table 5II.4. Over half of participants reported difficulties with ADLs (58%). Adults with functional difficulties were significantly older than those who denied difficulties. Specifically, adults in the youngest age group reported significantly less functional difficulties compared to adults in the oldest age group (p= .015), but not the middle-aged group (p= .083). Reports of functional difficulties were not significantly different between the middle and oldest age groups (p= .259). There were no significant differences between those who reported difficulties with ADLs and those who did not for clinical phenotypic or body composition parameters. A significantly lower duration of time spent in all PA parameters was found

in adults who reported functional difficulties. Functional difficulty was moderately correlated with total MVPA, but weakly correlated with all remaining variables (Table 5II.5).

Table 5II.1: Demographic information

		Total		HA		HB	
		n (%)		n (%)		n (%)	
		49 (100)		35 (71)		14 (29)	
Age groups	**18-32 years**	13 (26)		11 (85)		2 (15)	
	33-52 years	24 (49)		18 (75)		6 (25)	
	53-71 years	12 (25)		6 (50)		6 (50)	
Severity	**Severe**	43 (88)		30 (70)		13 (30)	
	Moderate	6 (12)		5 (83)		1 (17)	
Treatment history	**Prophylaxis**	43 (88)		30 (70)		13 (30)	
	On demand	6 (12)		5 (83)		1 (17)	
Age prophylaxis commenced by age group	**<3 years**	5 (13)		4 (80)		1 (20)	
	3-17 years	9 (24)		7 (78)		2 (22)	
	≥18 years	24 (63)		15 (63)		9 (37)	
History of inhibitors	**Inactive**	6 (12)		5 (83)		1 (17)	
	No history	43 (88)		30 (70)		13 (30)	
HCV history	**Previous history**	34 (69)		22 (65)		12 (35)	
	No history	15 (31)		13 (87)		2 (13)	
HIV history	**Positive**	13 (27)		12 (92)		1 (8)	
	Negative	36 (73)		23 (64)		13 (36)	
		Mean ± SD	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**	**Mean ± SD**	**Median (Q1, Q3)**
Age (years)		42 ± 13	44 (32, 52)	41 ± 13	39 (29, 50)	47 ± 14	48 (33, 56)
Age prophylaxis commenced (years)†		29 ± 19	26 (13, 49)	25 ± 19	23 (12, 42)	35 ± 19	41 (17, 52)
BMI (kg/m^2)		27.3 ± 4.5	27.0 (24.8, 29.6)	27.4 ± 4.8	26.8 (24.1, 30.6)	27.1 ± 3.9	28.0 (24.8, 29.2)
Waist circumference (cm)		94.0 ± 10.8	95.0 (87.7, 103.1)	93.3 ± 11.2	93.6 (83.5, 102.7)	95.8 ± 10.1	96.5 (91.7, 104.6)
Waist-height ratio		.54 ± .06	.55 (.49, .58)	.53 ± .07	.54 (.49, .58)	.55 ± .06	.55 (.54, .57)
ABR (bleeds per year)		3 ± 3	2 (1, 4)	3 ± 3	2 (0, 4)	2 ± 3	1 (1, 3)
HJHS‡	**Total**	27 ± 13	28 (20, 36)	27 ± 12	29 (20, 38)	28 ± 15	24 (20, 35)
	HJHS ankle	11 ± 5	12 (8, 15)	10 ± 6	11 (7, 14)	12 ± 5	12 (10, 15)
	HJHS knee	5 ± 6	4 (1, 9)	5 ± 5	4 (1, 9)	6 ± 7	3 (1, 10)
	HJHS elbow	8 ± 6	8 (2, 12)	8 ± 6	8 (3, 13)	6 ± 5	7 (1, 10)
	Global gait score	3 ± 1	4 (4, 4)	3 ± 1	4 (4, 4)	3 ± 1	4 (4, 4)
HJHS by age category‡	**18-32 years**	17 ± 13	20 (4, 23)	19 ± 12	21 (7, 26)	1 (raw value)§	
	33-52 years	28 ± 11	27 (21, 38)	31 ± 12	31 (21, 41)	21 ± 4	22 (18, 23)
	53-71 years	37 ± 10	34 (32, 46)	35 ± 6	32 (32, 40)	39 ± 12	35 (32, 53)

Continuous variables are presented as mean ± standard deviation and median (IQR- Q1, Q3); Categorical variables are presented as n (%). ABR Annualised Bleed Rate**; BMI** Body Mass Index**; HA** Haemophilia A **HB** Haemophilia B **HJHS** Haemophilia Joint Health Score**. † n= 38 (FVIII= 26; FIX= 12, remaining did not answer) ‡ n= 44 (no HJHS available for 5 participants with moderate haemophilia)**

Table 5II.2: Pain prevalence, analgesic requirements and functional difficulty prevalence by age group

		18-32 years		33-52 years		53-71 years		
		Yes	No	Yes	No	Yes	No	
Prevalence (n)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**p**
Acute pain (47)	34 (72)	10 (77)	3 (23)	17 (77)	5 (23)	7 (58)	5 (42)	.454
Chronic pain (48)	34 (71)	5 (39)	8 (61)	19 (83)	4 (17)	10 (83)	2 (17)	**.016***
Pharmacological analgesia (48)	44 (92)	11 (85)	2 (15)	23 (96)	1 (4)	10 (91)	1 (9)	.437
Difficulties with ADLs (48)	28 (58)	4 (31)	9 (69)	14 (61)	9 (39)	10 (83)	2 (17)	**.035***
Pharmacological analgesia (n= 29)								
COX-2 inhibitors	23 (79)	2 (67)	1 (33)	15 (83)	3 (17)	6 (75)	2 (25)	.665
Weak opioid analgesics†	11 (38)	1 (33)	2 (67)	7 (39)	11 (61)	3 (38)	5 (62)	1.000
Paracetamol	11 (38)	2 (67)	1 (33)	6 (33)	12 (67)	3 (38)	5 (62)	.627
Steroid injections	6 (21)	2 (67)	1 (33)	4 (22)	14 (78)	0	8 (100)	-
Strong opioid analgesics†	2 (7)	0	3 (100)	2 (11)	16 (89)	0	8 (100)	-
NSAIDs	1 (3)	0	3 (100)	1 (6)	17 (94)	0	8 (100)	-
Other†	3 (10)	1 (33)	2 (67)	1 (6)	17 (94)	1 (13)	7 (87)	-
Taking >1 analgesic medication	13 (45)	2 (67)	1 (33)	9 (50)	9 (50)	2 (25)	6 (75)	.459

Data are presented as n (%). Fischer's Exact analyses of pain and pharmacological analgesia by age group is presented due to expected cell counts less than five. (-) indicates test no statistical comparison interpreted due to very limited sample size. Missing data were excluded from the analyses as participants did not answer questions; ADLs Activities of Daily Living**; Cox-2** Cyclooxygenase-2**; NSAIDs** Non-steroidal anti-inflammatory drugs; **†Weak opioid analgesics=** E.g. Tramadol, Co-codamol; **Strong opioid analgesics=** E.g. Oxycodone, Morphine**; Other=** Gabapentin, lidocaine, herbal remedies, topical gels; *** statistically significant at α= .05 (two-tailed)**.

Figure 5II.2: Use of pharmacological analgesia by age group

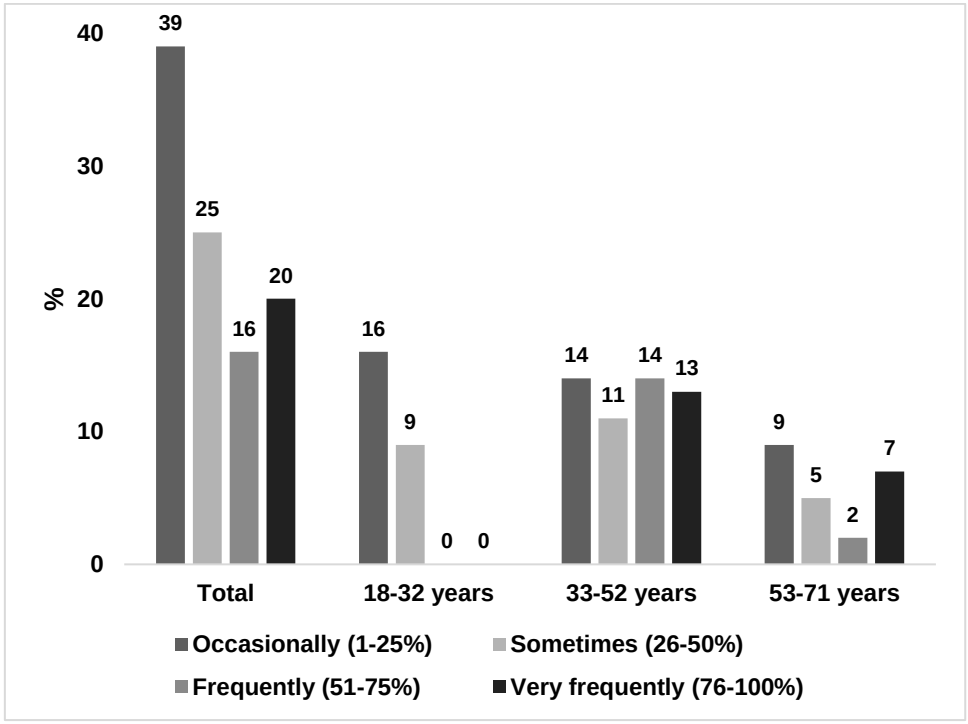


Table 5II.3: Causes and impact of pain

Causes of pain onset:	Acute pain n (%)	Chronic pain n (%)
Walking	13 (38)	29 (85)
Stair climbing	9 (26)	18 (53)
At night (such as waking you up/keeping you awake)	2 (6)	16 (47)
Resting	3 (9)	13 (38)
Weight bearing	5 (15)	22 (65)
Playing or participating in sports/exercise†	11 (32)	21 (62)
After falling or a trauma	16 (47)	3 (9)
Impact on activities and quality of life:	**Acute pain‡ n (%)**	**Chronic pain n (%)**
General Activity	22 (67)	26 (76)
Mood	16 (48)	23 (68)
Walking ability	24 (73)	29 (85)
Normal work (both outside the home and housework)	13 (39)	19 (56)
Attending school	1 (3)	0
Relations with others	5 (15)	9 (26)
Sleep	10 (30)	16 (47)
Enjoyment of life	16 (48)	23 (68)
Playing or participating in sports/exercise†	17 (52)	21 (62)
Lifting	14 (42)	13 (38)

Acute pain (n=34); Chronic pain (n=34). Data are presented as n (%); † Includes playing with children; ‡ Acute pain= 33 (1 participant did not answer)

Table 5II.4: Influences of demographic and lifestyle factors on pain and functional disability

	Acute pain (34)	No acute pain (13)	Chronic pain (34)	No chronic pain (14)	ADLs difficulty (28)	No ADLs difficulty (20)
Age (years)	44 (32, 51)	49 (31, 57)	45 (33, 55)	29 (23, 50)	45 (35, 58)	36 (25, 50)
Mean ranks	23.00	26.62	27.32	17.64	28.07	19.50
U	187.0		334.0		380.0	
p	.148		**.029***		**.036***	
ABR (bleeds per year)	2 (1, 5)	1 (0, 3)	2 (1, 4)	0 (0, 2)	2 (1, 5)	1 (0, 3)
Mean ranks	25.41	20.31	28.01	15.96	27.32	20.55
U	269.0		357.5		359.0	
p	.246		**.006***		.093	
Age prophylaxis commenced (years)†	23 (11, 43)	44 (23, 50)	32 (20, 51)	8 (1, 23)	34 (19, 52)	15 (7, 40)
Mean ranks	17.24	21.36	22.27	11.27	21.90	15.19
U	106.0		228.0		229.0	
p	.279		**.005***		.061	
HJHS‡	23 (19, 35)	32 (22, 35)	29 (21, 34)	22 (5, 35)	32 (21, 39)	22 (16, 35)
Mean ranks	20.30	24.50	23.63	17.79	24.35	18.41
U	144.0		236.5		282.0	
p	.316		.171		.129	
BMI (kg/m^2)	27.4 (24.6, 29.5)	26.8 (24.8, 31.9)	27.0 (24.8, 29.5)	27.4 (24.0, 33.0)	27.5 (24.8, 31.3)	27.1 (25.0, 28.7)
Mean ranks	24.06	23.85	24.04	25.61	25.46	23.15
U	223.0		222.5		307.0	
p	.962		.725		.572	
Waist Circumference (cm)§	95.0 (86.4, 104.6)	96.5 (88.9, 102.2)	95.0 (86.4, 101.9)	96.6 (86.5, 104.8)	98.5 (87.8, 104.6)	93.1 (88.9, 98.8)
Mean ranks	23.41	23.75	23.43	25.50	25.71	21.47
U	201.0		201.5		314.0	
p	.940		.643		.298	
Waist-Height Ratio§	.54 (.50, .58)	.57 (.50, .59)	.54 (.49, .58)	.55 (.50, .58)	.56 (.50, .60)	.54 (.49, .56)
Mean ranks	23.01	24.88	23.71	24.77	25.91	21.18
U	187.5		211.0		319.5	
p	.679		.812		.245	
Light PA (mins/wk)¶	2012 (1511, 2582)	1727 (1375, 2136)	1883 (1338, 2429)	1969 (1626, 2335)	1830 (1335, 2264)	2268 (1837, 2919)
Mean ranks	22.71	18.09	21.42	23.50	18.46	27.41
U	208.0		168.0		129.0	
p	.283		.626		**.022***	
MVPA (mins/wk)¶	204 (104, 265)	285 (196, 353)	202 (104, 271)	248 (198, 360)	164 (99, 242)	271 (223, 364)
Mean ranks	19.61	26.82	20.35	26.25	17.38	29.06
U	112.0		135.0		101.0	
p	.094		.167		**.003***	
Freedson MVPA (mins/wk)¶	31 (11, 78)	81 (27, 170)	28 (11, 96)	70 (40, 118)	28 (11, 77)	81 (33, 173)
Mean ranks	19.68	26.64	20.29	26.42	18.81	26.88
U	114.0		133.0		138.0	
p	.105		.150		**.039***	

Data are presented as median (IQR- Q1, Q3); ABR Annualised Bleed Rate **ADLs** Activities of Daily Living **BMI** Body Mass Index **HJHS** Haemophilia Joint Health Score **MVPA** Moderate-vigorous physical activity **PA** Physical Activity **mins/wk** Minutes per week**; † n= 36 (n-13 did not answer); ‡ n-5 with moderate haemophilia (no HJHS available); § n-1 for all domains; ¶ PA analysis n= 42 for acute pain and n= 43 for chronic pain and ADLs; * statistically significant at α= .05 (two-tailed)**.

Table 5II.5: Correlation analysis between categories of pain and functional difficulties and demographic variables

	Acute pain (47)		Chronic pain (48)		Difficulties with ADLS (48)	
	r_s	P	r_s	P	r_s	p
Age (years)	-.119	.424	.318	**.028***	.305	**.035***
ABR (bleeds per year)	.171	.251	.401	**.005***	.245	.093
Age prophylaxis commenced† (years)	-.183	.285	.471	**.003***	.312	.060
HJHS‡	-.157	.322	.211	.174	.234	.131
BMI (kg/m^2)	.007	.963	-.051	.729	.082	.578
Waist circumference (cm)§	-.011	.941	-.068	.648	.153	.303
Waist-Height Ratio§	-.062	.684	-.035	.815	.171	.249
Light PA (mins/wk)¶	.168	.289	-.075	.632	-.353	**.020***
MVPA (mins/wk)¶	-.261	.095	-.213	.170	-.460	**.002***
MVPA ≥10 minutes (mins/wk)¶	-.253	.106	-.222	.153	-.319	**.037***

ABR Annualised Bleed Rate **ADLs** Activities of Daily Living **BMI** Body Mass Index **HJHS** Haemophilia Joint Health Score **MVPA** Moderate-vigorous physical activity **PA** Physical Activity **mins/wk** Minutes per week r_s Spearman's Rho**; † n= 36 for acute pain and 37 for chronic pain/ difficulties with ADLS; ‡ n= 42 for acute pain and 43 for chronic pain/ difficulties with ADLS; § n-1 for all domains; ¶ n= 42 for acute pain and 43 for chronic pain/ difficulties with ADLS; * statistically significant at α= .05 (two-tailed)**.

5II.3.3.3 Target joints

There were no clinically diagnosed target joints in any participant according to the audit of ABR data, although self-reported target joint prevalence was examined according to age, and results are presented in Table 5II.6. Chronic pain resulting from target joints was reported by 58% and there was no significant association with age. When asked specifically about three or more spontaneous bleeds into any one joint within the previous six months (i.e. the clinical definition of a target joint), 23% answered yes, and age was not significantly associated. There was no significant association between self-perceived target joints and self-reported clinically defined target joints (Table 5II.7). Age, ABR, HJHS, body composition and PA parameters were not significantly different in participants who reported target joints compared to those who denied them (Table 5II.8), although they did commence prophylaxis at a significantly younger age.

Table 5II.6: Self-reported target joints by age groups

		n (%)	18-32 years n (%)	33-52 years n (%)	53-71 years n (%)	p
Self-perceived target joints	**Yes**	37 (76)	10 (77)	21 (88)	6 (55)	.131
	No	11 (22)	3 (23)	3 (12)	5 (45)	
	I do not know	1 (2)	-	-	1	
Chronic pain caused by target joints†	**Yes**	21 (58)	4 (44)	14 (67)	3 (50)	.571
	No	15 (42)	5 (56)	7 (33)	3 (50)	
≥3 spontaneous bleeds into one joint within 6 months‡	**Yes**	11 (23)	4 (31)	5 (25)	2 (18)	.905
	No	33 (69)	9 (69)	15 (75)	9 (82)	
	I do not know	4 (8)	-	3	1	

Categories are compared by age group using Fisher's Exact Test, 'I do not know scores' were excluded from the analysis. Data are presented as n (%); † n=36 (not applicable to 12 participants who answered no or do not know, one participant did not answer question); ‡ n= 48 (One participant did not answer); α= .05 (two-tailed).

Table 5II.7: Comparison of target joint reports

		Self-perceived target joints		p
		No	**Yes**	
		n (%)	**n (%)**	
Spontaneous bleeds (≥3) into any one joint in 6 months	**No**	9 (21)	24 (56)	0.407
	Yes	1 (2)	9 (21)	

Categories are compared using Fisher's Exact Test, 'I do not know scores' were excluded from the analysis. Data are presented as n (%). Complete data for both questions available for 43 participant; α= .05 (two-tailed).

Table 5II.8: Age, body composition, PA and clinical phenotype by self-perceived target joint reports

	Target joints (36) Median (Q1, Q3)	No target joints (11) Median Q1, Q3)	Mean ranks	U	p
Age (years)	39 (31, 50)	51 (32, 58)	22.73 vs. 30.45	138.0	.108
ABR (bleeds per year)	2 (1, 4)	1 (0, 7)	24.72 vs. 23.77	211.5	.842
Age prophylaxis commenced (years)†	23 (12, 38)	48 (40, 55)	17.63 vs. 27.79	50.5	**.029***
HJHS‡	27 (20, 35)	32 (21, 40)	22.09 vs. 24.64	114.5	.630
BMI (kg/m^2)	27.3 (23.8, 30.0)	25.8 (24.8, 29.0)	25.04 vs. 22.68	223.5	.624
Waist Circumference (cm)	95.0 (84.7, 102.2)	93.5 (92.3, 104.5)	23.75 vs. 24.82	189.0	.833
Waist-Height Ratio	.54 (.49, .58)	.55 (.52, .57)	23.42 vs. 25.91	177.0	.611
Light PA (mins/wk)§	1931 (1530, 2544)	1747 (1375, 2232)	23.38 vs. 18.00	220.0	.221
Moderate PA (mins/wk)§	221 (113, 316)	183 (148, 264)	22.78 vs. 19.73	201.0	.486
Vigorous PA (mins/wk)§	0 (0, 1)	0 (0, 8)	21.19 vs. 24.36	150.0	.483
MVPA (mins/wk)§	221 (113, 317)	224 (148, 271)	22.34 vs. 21.00	187.0	.759
MVPA of at least 10-minute bouts (mins/wk)§	38 (11, 97)	77 (0, 160)	21.31 vs. 24.00	154.0	.539

Between group differences analysed using Mann-Whitney U test; Data are presented as median (IQR- Q1, Q3); BMI Body Mass Index **HJHS** Haemophilia Joint Health Score **MVPA** Moderate-vigorous physical activity **PA** Physical Activity **mins/wk** Minutes per week**; 'I do not know' scores excluded from analysis; † n-10 due to missing data; ‡ n-4 as no HJHS available for patients with moderate haemophilia; § PA analysis n= 43; * statistically significant at α= .05 (two-tailed).**

5II.4 Discussion

This study highlights patient lived experiences of pain associated with haemophilic arthropathy, and the resultant impact on ADLs and PA. High rates of acute pain, chronic pain and functional disability were reported. Age was significantly associated with more advanced haemophilic arthropathy, chronic pain and functional difficulties. Lower levels of objectively measured PA were significantly associated with functional difficulties. Adults who reported chronic pain commenced prophylaxis at a significantly later age, and more frequent analgesic requirements were also evident in older adults. Chronic pain attributable to self-perceived target joints was prevalent, however a disparity between self-perceived 'target joints' and clinically defined target joints was also identified.

5II.4.1 Chronic pain

The considerable levels of pain reported in this study are similar to previous studies who have reported a high prevalence of both acute and chronic pain in other populations with haemophilia (Kempton et al., 2018, Lorenzato et al., 2019). Specifically, the prevalence of chronic pain in adults with moderate and severe haemophilia from the present cohort was far higher than the prevalence of chronic pain in the general Irish population, which is estimated to be between 13 and 36% (Breivik et al., 2006, Raftery et al., 2011). Chronic pain in particular was significantly related to older age and later commencement of regular prophylaxis, which reflects the impact of improved treatments in more recent years on bleeds, severity of haemophilic arthropathy and associated pain in younger people with haemophilia (Manco-Johnson et al., 2017a, Manco-Johnson et al., 2017b). Although limited data was available regarding the age at which prophylaxis was commenced in this cohort, the majority of participants were treated with secondary or tertiary prophylaxis. Future comparisons with younger cohorts on primary prophylaxis and novel treatments would be of interest to ascertain the impact of these therapies on haemophilic arthropathy and resultant pain. Additionally, further comparison is warranted in populations without optimal access to prophylaxis.

Interestingly, self-reported target joints defined by the clinical definition were reported by some participants despite non-existent clinically diagnosed target joints within the entire cohort. Chronic pain was perceived in part to be attributable to target joints, however a disparity between self-perceived and self-reported clinically defined target joints was also highlighted. Younger adults reported a significantly higher prevalence of current target joints, despite a lower recall of clinically defined target joints. A disconnect between the clinical definition of a target joint and what patients identify as their 'target joint' is not unexpected as perceptions of problematic joints resulting from haemophilic arthropathy are more common than frequent spontaneous haemarthroses, especially in patients treated with secondary or tertiary prophylaxis. This also reflects the difficulty in the differential diagnosis of spontaneous haemarthroses versus an exacerbation of haemophilic arthropathy.

5II.4.2 Haemophilic arthropathy and pain

The ABR was significantly higher in participants who reported chronic pain. Additionally, as expected, older adults demonstrated significantly more advanced haemophilic arthropathy compared to younger adults. Haemophilic arthropathy is of course a major cause of pain for many PwMSH, however the HJHS did not differ significantly by categories of pain or functional difficulty. As the HJHS was developed for children and younger people with haemophilia (Hilliard et al., 2006), the interpretation of the analysis of haemophilic arthropathy in older adults from the present study is limited. In addition to the complex, multi-faceted nature of haemophilia-related pain, and the potential variation in phenotypic presentation, this confirms that the HJHS is not fully reflective of the severity of pain and disability experienced by individuals. Conflicting evidence has been described between the correlation of pain symptoms and the severity of radiographically measured haemophilic arthropathy in people with haemophilia (Wallny et al., 2002, van Genderen et al., 2006), which has also been demonstrated extensively in other arthritic populations, including osteoarthritis (Felson et al., 2000, Wang et al., 2018). Study findings therefore support the concept that traditional measures of joint health do not fully reflect the severity of pain and disability experienced by an individual, and the use of functional and patient-reported outcomes are additionally important in the treatment and management of chronic haemophilic arthropathy in PwMSH.

5II.4.3 Analgesic requirements

Holistic pain coping strategies and the optimisation of pain management have been advised to improve health-related quality of life for people with haemophilia who experience chronic pain (Auerswald et al., 2016), however the frequent use of pharmacological analgesia was an important finding in this study. Despite discouragement of the long-term use of COX-2 inhibitors and other pharmacological analgesia, it has been suggested that the benefits outweigh the potential for unfavourable side effects in the short-term when appropriately managed and monitored (Arachchillage and Makris, 2016). However, the long-term pharmacological management of pain is limited amongst older adults who may develop other cardiovascular risk factors with age. Thus, individually tailored PA and exercise programmes are ever more pertinent for PwMSH across the lifespan, as these therapies offer multi-faceted benefits, including the potential to treat and manage chronic pain (Geneen et al., 2017), reduce cardiometabolic risk factors (Bull et al., 2020) and even optimise the potential for successful post-operative outcomes for those who require orthopaedic joint replacement surgery (Santa Mina et al., 2014). Analgesia was prescribed in the tertiary healthcare setting in this cohort, however information regarding the use of ‘over the counter’ analgesia and that prescribed in the primary healthcare setting should also be examined in future studies.

5II.4.4 Pain and physical activity

Findings that pain was not significantly related to objectively measured PA are in keeping with similar research by Timmer et al. (2020), who found no significant relationship between pain and PA measured by accelerometry in adults with haemophilia. However, the possibility of a type II error

cannot be ignored in light of the small sample size in the present study. Despite this, time spent in any intensity of PA was significantly lower in individuals who reported having difficulties with ADLs. This discordance may be explained by more severe levels of arthropathy experienced by older adults compared to younger adults who commenced prophylaxis at an earlier age, and thus have lower levels of functional difficulties. Participants further reported that pain was commonly caused by certain functional and physical activities, and pain simultaneously impacted various aspects of quality of life. Any causal inference between pain, functional disability and PA in an individual is difficult to establish due to the complex interrelationship between these parameters, however pain and functional disability commonly present barriers to exercise and PA. Some evidence has been found to support water and land-based exercise for the treatment and management of pain in people with haemophilia, although more studies of improved methodological quality are recommended by McLaughlin et al. (2020).

5II.4.5 Pain and body composition

Increased mechanical stress may exacerbate pain, and increased adiposity is also speculated to contribute to systemic inflammation via increased levels of adipokines, which may also compound pain (Arranz et al., 2013, Daïen and Sellam, 2015). Elevated BMI has been identified as a significant determinant of chronic pain in individuals with osteoarthritis and rheumatoid arthritis (Arranz et al., 2013, Ajeganova et al., 2013, Daïen and Sellam, 2015), although surprisingly, body composition parameters were not significantly related to pain or functional difficulties in adults with HA in this study, despite 68% being classified as overweight or obese. This is in keeping with the prevalence of overweight and obesity in the general male Irish population (~68%) (Healthy Ireland, 2015). Weight loss via diet, exercise and behaviour modification has been shown to reduce pain, functional disability and inflammation in other disease populations, and despite the study findings, may offer a potential alternative treatment for pain in PwMSH (Janke et al., 2007, Gleeson et al., 2011).

5II.4.6 Limitations

Given the cross-sectional nature of this study, there is no means to establish temporality or causality between variables. In addition to the small sample size, another limitation of this study was that demographic information about non-responders was not available, therefore a potential non-response bias could not be avoided. Findings based on self-reported methods may also be affected by potential recall bias. Lastly, although the PROBE questionnaire was the most appropriate tool to measure pain for this study, it did not grade the intensity of pain or assess the additional multi-faceted aspects of haemophilia-related pain.

5II.5 Conclusion

In conclusion, this study found a high prevalence of acute and chronic pain, and functional disability amongst Irish adults with moderate and severe haemophilia impacted by chronic haemophilic arthropathy. Older adults had more years without adequate treatment especially as children,

therefore the extent of pain and functional impairment appears to be age-dependent and may also affect PA participation amongst other aspects of quality of life. This has potential implications for the physical health and wellbeing of the ageing population with haemophilia, and requires further investigation. Additionally, the frequent use and efficacy of pharmacological analgesia amongst different age groups, and the influence of treatment regimens and novel therapies on the development of chronic pain across the lifespan, warrants consideration in future longitudinal studies.

Chapter 6: Study IV: A follow-up of physical activity in adults with moderate and severe haemophilia during the Covid-19 pandemic

6.1 Introduction

Coronavirus disease 2019 (Covid-19) is a novel virus caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Tsang et al., 2020, Zhu et al., 2020). The Covid-19 global pandemic was officially declared by the World Health Organisation on the 11th of March 2020 in response to increasing rates of disease transmission globally (Cucinotta and Vanelli, 2020). Subsequently, international governments enforced significant social distancing restrictions on society, commonly referred to as 'lockdown', in order to reduce the rate of Covid-19 transmission (Stockwell et al., 2021).

The initial lockdown in Ireland came into effect on the 27th of March 2020 when all education and non-essential work settings were advised to close (NPHET, 2021). Citizens were advised not to leave their homes other than for essential purposes, or for exercise within a 2km radius of their house (NPHET, 2021). All non-essential surgeries, health procedures and services were postponed, and access to hospital and clinical sites was restricted to essential frontline healthcare staff (Holohan, 2020). Many hospital services and clinics were adapted to online and telephone consultations, commonly referred to as 'Telehealth', including the Irish haemophilia healthcare service (O'Donovan et al., 2020). Consequently, in-person research activity for this thesis was disrupted, and plans to conduct a pilot study involving an objective assessment of cardiorespiratory fitness in adult people with moderate and severe haemophilia (PwMSH) were postponed. As the pandemic progressed, ongoing restrictions continued to impact the ability to conduct in-person research activity, therefore the study plan was adapted in September of 2020.

In addition to the numerous health benefits associated with regular physical activity (PA) discussed throughout this thesis, participation in regular PA has also been strongly associated with a reduced risk of severe illness and death from Covid-19 (Lee et al., 2021, Sallis et al., 2021). Furthermore, regular PA has been associated with lower levels of depression and anxiety during the Covid-19 pandemic (Violant-Holz et al., 2020, Wolf et al., 2021), which highlights an important role for PA in dealing with stress and mental health issues during challenging circumstances. Lockdowns and stay at home orders throughout the pandemic have presented challenges for the general population in achieving a physically active lifestyle, and therefore the potential to reap the numerous associated health benefits of PA.

A lack of time and motivation for PA are established barriers to being active. Such barriers may have become more or less burdensome during the pandemic as a result of working and schooling from home policies, in addition to less opportunities for socialising. Individuals may therefore have had more free time and motivation for exercise. Furthermore, opportunities to take up new forms of exercise were also more accessible due to an increase in online exercise platforms, such as online classes for strength and aerobic training, yoga and Pilates (Faulkner et al., 2021, Murphy et al., 2021, Forde et al., 2021). Equally, barriers to PA may have increased, especially for the elderly and

medically vulnerable who are at an increased risk of severe Covid-19 illness and subsequently higher rates of hospitalisation, intensive care unit admission and mortality (Semenzato et al., 2021, Bennett et al., 2021). Increased caregiving demands on families, working demands on frontline workers, and staffing shortages across a variety of sectors may also have resulted in less time to engage in regular leisure time PA for many. Variable levels of engagement in PA throughout the course of the pandemic have been demonstrated across various populations, with the majority indicating a decline in PA particularly during the initial phases of lockdown (Violant-Holz et al., 2020, Bu et al., 2021, Cho et al., 2021, de Boer et al., 2021, Faulkner et al., 2021, Forde et al., 2021, Murphy et al., 2021, Stockwell et al., 2021, Wolf et al., 2021).

In order to provide insights regarding the impact of the Covid-19 pandemic on PA in Irish adult PwMSH, a follow-up study of PA in participants from the original study was conducted remotely. This provided an opportunity to determine if current PA behaviour and awareness had changed during the interim study period. Additionally, this opportunity could potentially inform more accurate future directions based on up-to-date conclusions about PA behaviour in Irish PwMSH, particularly in the present day as Ireland has emerged from pandemic restrictions.

6.1.1 Aim

The primary aim of this study is to conduct a follow-up assessment of PA in adult PwMSH from the original study (See Chapter 3). Secondary aims are to determine if PA awareness had changed in the group since the original assessment, as well as to determine the impact of the Covid-19 pandemic on PA.

6.1.2 Objectives

6.1.2.1 Primary objective

1) To compare current PA with previously measured PA in adult PwMSH from the original study.

6.1.2.2 Secondary objectives

1) To determine PA awareness in study participants since the original assessment.

2) To determine the impact of the Covid-19 pandemic on PA in PwMSH.

6.2 Methodology

6.2.1 Study design and recruitment

Recruitment and data collection for this follow-up study took place between June and December 2021. Only participants who had consented and participated in the original research assessment were eligible for inclusion. Therefore, all participants were males ≥18 years with diagnosed moderate or severe haemophilia A (HA) or haemophilia B (HB), without active inhibitors. Of the 54 participants who were originally assessed, 49 were accessible for follow-up. A participant information leaflet was

posted to previous participants (See Appendix XXV). Participation was voluntary and participants were contacted subsequently to determine follow-up uptake. Study procedures involved sending an ActiGraph accelerometer and an anonymised questionnaire to the participant, including a pre-paid stamped and addressed return envelope. This study received ethical approval from St. James's Hospital/ Tallaght University Hospital Joint Research Ethics Committee (Appendix VI).

6.2.2 Demographics and outcome measures

6.2.2.1 Demographic information

Demographic information already available from the original research assessment included the type and severity of haemophilia, the age at which prophylaxis was commenced, previous treatment history, history of inhibitors and comorbid history of Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV). Current age and treatment status were updated as appropriate.

6.2.2.2 Outcome measures

- PA was objectively measured using the ***ActiGraph GT3X-BT accelerometer (ActiGraph Corp, Pensacola, Florida, USA)*** which was posted to the participant. According to standardised procedures, participants were asked to wear the monitor for one week, and raw data was downloaded, cleaned and analysed using the ActiLife software (Version 6.13.4) (See section 2.6.3.1).
- PA awareness and the impact of the Covid-19 pandemic on PA were assessed using a ***Longitudinal Follow-up Questionnaire*** (See section 2.6.6.3, Appendix XVI). This questionnaire involved a series of questions regarding PA awareness and engagement since the original assessment. Participants were additionally asked to recall how their PA was compared to normal during the various phases of lockdown and eased restrictions during the pandemic in Ireland (Figure 6.1), and to rate their answer using a Likert scale. This questionnaire also included a section regarding self-reported PA engagement over the previous year using the ***Modifiable Activity Questionnaire*** (See section 2.6.3.2).

Figure 6.1: Timeline of the pandemic in Ireland

6.2.3 Statistical methods

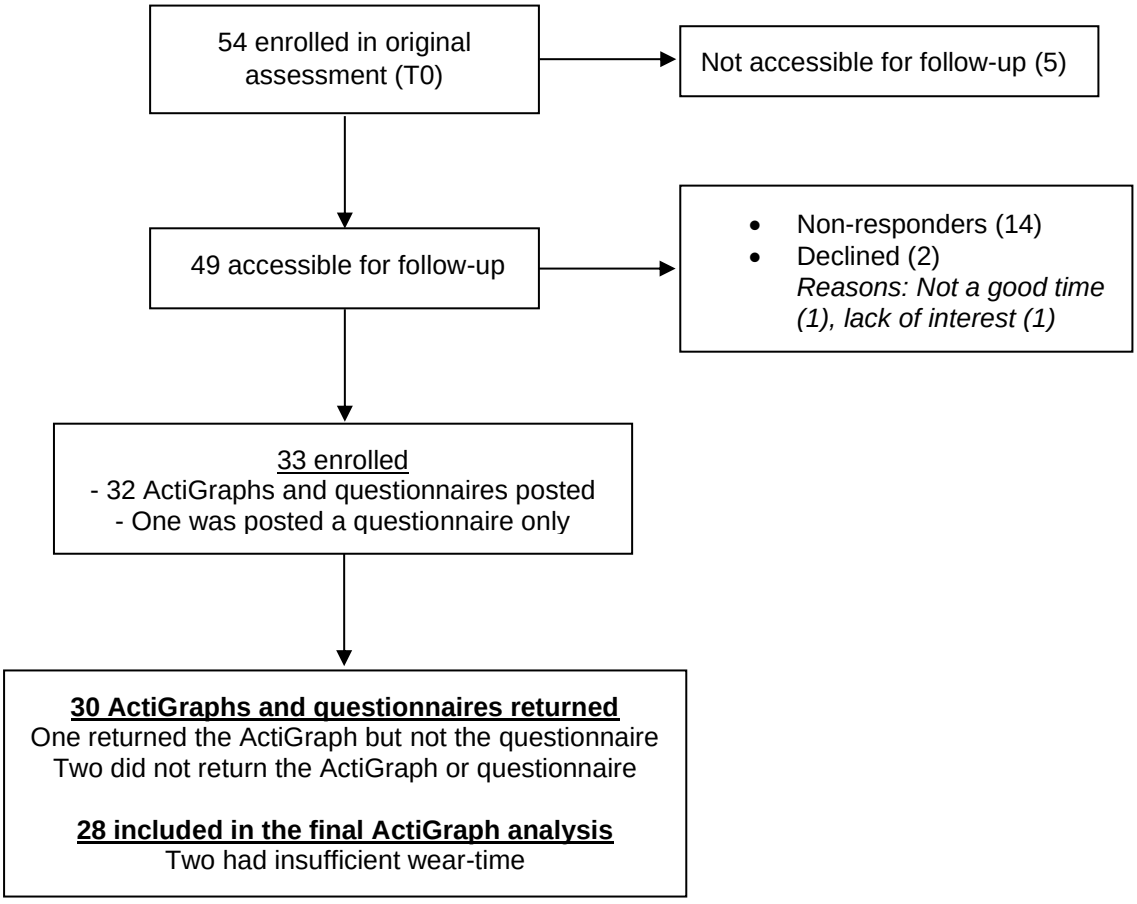
Data were analysed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.). Data distribution was assessed using the Shapiro-Wilk test and visual inspection of histograms, normal Q-Q plots and box and whisker plots. Continuous variables are described as mean ± standard deviation, and median and interquartile range (IQR: Q1, Q3). Non-parametric statistical tests were chosen due to the skewed distribution of the data. Continuous data were compared between groups using the Mann-Whitney U test. Continuous data were compared within the group at two time-points labelled T0 (at original assessment) and T1 (at follow-up assessment). Medians were compared within the group using the Wilcoxon Signed Rank test or the Sign test, as appropriate. An underlying assumption of the Wilcoxon Signed Rank test is that the distribution of the differences between medians is symmetrical (Laerd, 2015c). Where this assumption is violated, the Sign test, which does not require this assumption, is recommended for interpreting the null hypothesis (i.e. the median of the paired differences in the dependent variable is equal to zero) (Laerd, 2015b). Categorical data are described using frequencies and percentages. Categorical variables were compared using Fisher's exact test as expected cell counts were less than five. Weekly PA was categorised according to the achievement of PA guidelines in both the total duration of moderate-vigorous PA (MVPA), and the duration of MVPA achieved via Freedson bouts (i.e. sustained bouts of MVPA ≥10 minutes). Guidelines recommend that adults should undertake 150-300 minutes of moderate intensity PA, or 75-150 minutes of vigorous intensity PA, or an equivalent combination of MVPA per week (Bull et al., 2020). Missing data were excluded from analyses and are highlighted throughout the results with explanations. Statistical significance was considered at alpha (α)= .05 (two-tailed). Where p=.000, it is implied that p is <.0005 as per SPSS guidance (IBM, 2020b).

6.3 Results

6.3.1 Recruitment flow

Of the 54 participants originally assessed, 49 were accessible for recruitment and 33 enrolled, representing a 67.3% uptake. Ultimately, 30 questionnaires were completed, indicating a 61.2% follow-up rate. Wear-time inclusion criteria for the ActiGraph were met by 28 participants (i.e. ≥10 hours on ≥4 days, including one weekend day), indicating a 57.1% follow-up rate. The median number of years until follow-up was 2.99 [IQR: (2.91, 3.08); Range: 1.55-3.30] years. Recruitment flow and reasons for exclusion and non-participation are presented in Figure 6.2.

Figure 6.2: Recruitment flow chart



6.3.2 Demographics

Demographic information of participants included in the analysis is presented in Table 6.1. HA accounted for 73.1% of participants with severe haemophilia (86.7%). A small proportion of participants had moderate HA (13.3%). All remaining participants had severe HB. The median age of the group was 47 (36, 55) years. There was no significant difference in age between participants with HA and HB [mean ranks: 14.04 vs. 20.29 (respectively); U= 114.0; p= .107]. All participants with severe haemophilia, and one participant with moderate HA were treated with prophylaxis. The median age at which prophylaxis was commenced was 26 (14, 49) years, and 60.0% commenced prophylaxis at 18 years or older. Participants with HB commenced prophylaxis at a significantly older age compared to participants with HA [mean ranks: 18.25 vs. 11.34 (respectively); U= 88.5; p= .043]. Extended half-life factor products were used by 43.3% at T1, compared to 86.7% at T0. Amongst participants with HA, 56.5% had switched from an extended half-life product to a non-factor product between T0 and T1. A very small proportion of participants with severe HB (n= 2) had switched to other haemophilia treatment options. A previous history of HCV was prevalent in 76.7%, and 33.3% were HIV positive. A previous history of inhibitors was prevalent in 16.7%, but inhibitors were not active during the study period.

6.3.3 Physical activity

Details of objectively measured PA at T0 and T1 are presented in Table 6.2. Wear-time was comparable between the two time-points. There were no significant differences in any parameters of PA within the group. Achievement of PA guidelines increased from 67.9% at T0 to 75.0% at T1 (p= .646). Guidelines achieved in Freedson bouts of MVPA ≥10 minutes also increased from 17.9% at T0 to 28.6% at T1 (p= .123). Details of PA guideline achievement are presented in Table 6.3.

Self-reported PA over the previous year was assessed using the Modifiable Activity Questionnaire, and is presented in Table 6.4. Various types of PA were undertaken with walking, cycling and gardening being the most common. The median number of activities undertaken per participant was 4 (2, 4). The median number of months of PA engagement was 8 (7, 10). The median volume of PA per month (i.e. the product of duration in minutes by frequency measured in days) was 2000 (1155, 2580) minutes per month.

6.3.4 Physical activity awareness

Results regarding PA awareness since T0 are presented in Table 6.5 Participation in the original research assessment made 76.7% of the group more aware of their PA behaviour. Participation also made 66.7% want to become more physically active. New exercise programmes or sports were commenced by 30.0%, and included a variety of types of PA, such as sea swimming and online exercise classes. Knowledge of the PA guidelines was claimed by 36.7%, and 9.1% of these participants cited guidelines fully and correctly including both duration and intensity of PA, whilst

90.9% cited guidelines partially correctly, stating only the duration per week, duration per day or intensity of PA alone.

Table 6.1: Demographic information

n (%)		Total		Haemophilia A		Haemophilia B	
		30 (100)		23 (76.7)		7 (23.3)	
		Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)
Age (years)		46 ± 13	47 (36, 55)	44 ± 12	43 (35, 53)	53 ± 12	56 (45, 58)
Age prophylaxis commenced (years)†		30 ± 19	26 (14, 49)	26 ± 18	23 (12, 40)	42 ± 15	47 (32, 53)
		n (%)		n (%)		n (%)	
Age group	21-36 years	8 (26.7)		7 (87.5)		1 (12.5)	
	37-53 years	13 (43.3)		11 (84.6)		2 (15.4)	
	54-74 years	9 (30.0)		5 (55.6)		4 (44.4)	
Severity	Severe	26 (86.7)		19 (73.1)		7 (26.9)	
	Moderate	4 (13.3)		4 (100)		0	
Treatment	Prophylaxis	25 (83.3)		20 (80.0)		5 (20.0)	
	On demand	3 (1.0)		3 (100)		0	
	Other	2 (6.7)		0		2 (100)	
Age group prophylaxis commenced	<3 years	1 (4.0)		1 (100)		0	
	3-17 years	9 (36.0)		8 (88.9)		1 (11.1)	
	≥18 years	15 (60.0)		10 (66.7)		5 (33.3)	
Inhibitors	Previous history	5 (16.7)		4 (80.0)		1 (20.0)	
	No history	25 (83.3)		19 (76.0)		6 (24.0)	
Hepatitis C Virus	Previous history	23 (76.7)		16 (69.6)		7 (30.4)	
	No history	7 (23.3)		7 (100)		0	
Human Immunodeficiency Virus	Positive	10 (33.3)		9 (90.0)		1 (10.0)	
	Negative	20 (66.7)		14 (70.0)		6 (30.0)	
		T0	T1	T0	T1	T0	T1
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment product	Standard half-life	2 (6.7)	0	2 (100)	0	0	0
	Extended half-life	26 (86.7)	13 (43.3)	19 (73.1)	8 (61.5)	7 (26.9)	5 (38.5)
	Non-factor	2 (6.7)	15 (50.0)	2 (100)	15 (100)	0	0
	Other	0	2 (6.7)	0	0	0	2 (100)

Continuous variables are presented as mean ± standard deviation and median (IQR: Q1, Q3). Categorical variables are presented as n (%). T0 Original assessment **T1** Follow-up assessment**; † n= 25 as five participants did not answer question**

Table 6.2: Physical activity compared between T0 and T1 (n=28)

	T0 Median (Q1, Q3)	T1 Median (Q1, Q3)	Median of differences	p
Light PA (mins/wk)	1993 (1592, 2462)	1870 (1671, 2393)	-31	.850†
Moderate PA (mins/wk)	206 (104, 337)	201 (134, 424)	13	.850†
Vigorous PA (mins/wk)	0 (0, 2)	0 (0, 3)	0	.332†
MVPA (mins/wk)	211 (104, 338)	212 (134, 424)	14	.850†
Freedson MVPA (mins/wk)§	42 (11, 113)	74 (15, 239)	-4	.690†
Weekdays with wear-time (days)	5 (5, 6)	5 (5, 6)	0	.451‡
Weekend days with wear-time (days)	2 (2, 2)	2 (2, 2)	0	.414‡
Average wear-time per day (hours)	14.13 (13.36, 14.43)	14.30 (13.42, 15.36)	.46	.186†
	Total MVPA n (%)		**Freedson MVPA§ n (%)**	
Positive differences	15 (53.6)		11 (39.3)	
Negative differences	13 (46.4)		14 (50.0)	
No differences	0		3 (10.7)	

Values are presented as median (IQR: Q1, Q3) or n (%) as appropriate; mins/wk Minutes per week **MVPA** Moderate-Vigorous Physical Activity **PA** Physical Activity **T0** Original assessment **T1** Follow-up assessment**; † Analysed using the Sign test; ‡ Analysed using the Wilcoxon Signed Rank test; § Freedson MVPA= Sustained MVPA accumulated in bouts of ≥10 minutes; α = .05 (two-tailed).**

Table 6.3: Physical activity guidelines achievement compared between T0 and T1

		MVPA guidelines achieved† [T1; n (%)]		
		No	**Yes**	**Total**
MVPA guidelines achieved† [T0; n (%)]	**No**	3 (10.7)	6 (21.4)	9 (32.1)
	Yes	4 (14.3)	15 (53.6)	19 (67.9)
	Total	7 (25.0)	21 (75.0)	28 (100)
Positive differences		6 (21.4)		
Negative differences		4 (14.3)		
No differences		18 (64.3)		
		Freedson MVPA guidelines achieved‡ [T1; n (%)]		
		No	**Yes**	**Total**
Freedson MVPA guidelines achieved‡ [T0; n (%)]	**No**	18 (64.3)	5 (17.8)	23 (82.1)
	Yes	2 (7.1)	3 (10.7)	5 (17.8)
	Total	20 (71.4)	8 (28.6)	28 (100)
Positive differences		5 (17.9)		
Negative differences		2 (7.1)		
No differences		21 (75.0)		

Values are presented as n (%); MVPA Moderate-Vigorous Physical Activity **T0** Original assessment **T1** Follow-up assessment**; † At least 150 minutes per week of MVPA ‡ At least 150 minutes per week of MVPA achieved in Freedson bouts sustained for ≥10 minutes**

Table 6.4: Self-reported physical activity over the previous year (n= 30)

Type of physical activity	n (%)	Frequency (months per year) Median (min-max)	Frequency (times per month) Median (min-max)	Duration (minutes each time) Median (min-max)
Cycling	12 (40.0)	7 (3-12)	5 (4-20)	60 (20-90)
Walking for exercise	24 (80.0)	12 (6-12)	20 (2-31)	60 (20-420)
Gardening/ Yard work	13 (43.3)	8 (5-12)	4 (1-16)	60 (30-180)
Strength/ Weight training	6 (20.0)	8 (3-12)	11 (6-20)	40 (15-80)
Gym	4 (13.3)	7 (3-12)	7 (4-20)	45 (20-80)
Calisthenics/ Toning exercises	1 (3.3)	7 (Raw data)	20 (Raw data)	20 (Raw data)
Swimming	8 (26.7)	4 (3-12)	8 (3-30)	40 (20-60)
Water/Coal hauling	4 (13.3)	3 (3-7)	10 (3-10)	10 (5-120)
Hiking	3 (10.0)	5 (4-10)	2 (1-2)	100 (30-300)
Hurling	1 (3.3)	5 (Raw data)	4 (Raw data)	60 (Raw data)
Wood-chopping	6 (20.0)	4 (3-7)	6 (2-10)	60 (20-180)
Football/ Soccer	1 (3.3)	(1 DNA)	(1 DNA)	(1 DNA)
Fishing	5 (16.7)	5 (4-9)	4 (3-8)	120 (60-180)
Golf	3 (10.0)	9 (3-12)	6 (3-8)	260 (120-400)
Bowling	3 (10.0)	3 (2-4)	3 (Raw data; 2 DNA)	60 (Raw data; 2 DNA)
Badminton	1 (3.3)	3 (Raw data)	3 (Raw data)	120 (Raw data)
Stair master	2 (6.7)	6 (5-7)	11 (2-20)	20 (20-20)
High intensity interval training	1 (3.3)	7 (Raw data)	20 (Raw data)	20 (Raw data)
Hunting	2 (6.7)	4 (1-6)	7 (6-8)	150 (120-180)
Yoga/ Pilates	2 (6.7)	6 (3-8)	4 (4-4)	60 (30-90)
Jogging	2 (6.7)	10 (7-12)	20 (Raw data; 1 DNA)	20 (Raw data)
Farming/ Manual labour	2 (6.7)	9 (Raw data; 1 DNA)	26 (Raw data; 1 DNA)	(2 DNA)
Archery	1 (3.3)	3 (Raw data)	10 (Raw data)	60 (Raw data)
Dancing	1 (3.3)	5 (Raw data)	5 (Raw data)	30 (Raw data)
Basketball	1 (3.3)	3 (Raw data)	5 (Raw data)	60 (Raw data)

Continuous values are presented as median (Range; min-max); Categorical values are presented as n (%). Raw values are reported where n= 1. DNA Indicates the number of participants that did not answer

Table 6.5: Physical activity awareness since T0 (n= 30)

Did your participation in the iPATH Physical Activity Study make you more aware of your physical activity habits?	n (%)
A lot more aware	6 (20.0)
Somewhat more aware	17 (56.7)
My awareness did not change	7 (23.3)
My participation in the iPATH Physical Activity Study made me want to…	
Become a lot more physically active	6 (20.0)
Become somewhat more physically active	14 (46.7)
Maintain my current activity levels	10 (33.3)
Have you participated in any new exercise programme or sport in the past year?	
Yes	9 (30.0)
No	21 (70.0)
If yes, please specify:	
Fishing	1 (3.3)
Gym	3 (10.0)
Home exercise programme	1 (3.3)
Online physiotherapy exercise class	1 (3.3)
Sea swimming	2 (6.7)
Stationary cycling and rounders	1 (3.3)
Not applicable	21 (70.0)
Do you know how much physical activity adults are recommended to undertake according to the global guidelines?	
Yes	11 (36.7)
No	16 (53.3)
Did not answer	3 (10.0)
Physical activity guidelines correctly stated (n=11)	
Fully correct	1 (9.1)
Partially correct	10 (90.9)

6.3.5 Impact of Covid-19 pandemic on physical activity

The impact of the Covid-19 pandemic on self-reported PA throughout the various phases of lockdown and easing of restrictions is presented in Table 6.6. The trend of these reports throughout the pandemic is visually presented in Figure 6.3. Decreased PA compared to normal was reported by 36.6% and 37.9% during the initial lockdowns when exercise was not permitted beyond a 2 and 5km radius from home, respectively. Decreased PA was reported more commonly during the second lockdown, but reduced slightly with the second easing of restrictions in December 2020. An increased decline in PA engagement is noted again during the third lockdown, with 42.9% reporting less PA compared to normal. Decreased PA reports declined with the third phase of eased restrictions.

No difference in PA was reported by 40.0% of participants during the initial lockdown, and trends of these reports increased as the pandemic progressed, including during periods of eased restrictions. Reports of no differences in PA decreased substantially during the third lockdown and the third phase of eased restrictions.

The smallest proportion of participants (23.3%) reported an increase in PA during the initial lockdown. Reports of increased PA decreased by the first phase of eased restrictions, which continued during the second lockdown. A positive trend in increased PA compared to normal was evident from the second phase of eased restrictions, and increased PA was reported by 46.4% by the third phase of eased restrictions. Participants were also asked about the impact of the pandemic on their mobility, functional ability and pain during lockdown. Results are described in Table 6.7.

Alternative explanations for decreased PA during the pandemic, other than the impact of the pandemic itself, were provided by 26.7%. Reasons included recovering from surgery or injury, as well as increased work and parenting demands. Participants were asked about their concerns for PA over the coming year. These concerns were classified as themes and are presented in Table 6.8. The most common concerns were pain-related. Lack of access to resources, especially to swimming pools and gyms, as well as desires to increase and maintain PA were also reported. Other concerns highlighted were related to arthropathy, fatigue, mobility, lack of time and weight gain. When asked about any other comments regarding the impact of the pandemic on PA, function or pain, both negative and positive sentiments about the impact of commuting to work on PA were reported. Other reports included that a lack hospital services available during the pandemic negatively impacted on pain, and a negative impact of working from home on motivation.

Table 6.6: Impact of the Covid-19 pandemic on self-reported physical activity (n= 30)

Pandemic phase	Date period	A lot less active	Somewhat less active	No difference	Somewhat more active	A lot more active
		n (%)	n (%)	n (%)	n (%)	n (%)
Lockdown 1 (2km)	**27th Mar-4th May 2020**	4 (13.3)	7 (23.3)	12 (40.0)	3 (10.0)	4 (13.3)
Lockdown 1 (5km)†	**5th-17th May 2020**	3 (10.3)	8 (27.6)	13 (44.8)	2 (6.9)	3 (10.3)
Eased restrictions 1	**18th May- local restrictions 2020**	5 (16.7)	7 (23.3)	14 (46.7)	3 (10.0)	1 (3.3)
Lockdown 2‡	**21st Oct-30th Nov 2020**	2 (7.1)	10 (35.7)	14 (50.0)	1 (3.6)	1 (3.6)
Eased restrictions 2‡	**1st-29th Dec 2020**	4 (14.3)	7 (25.0)	14 (50.0)	2 (7.1)	1 (3.6)
Lockdown 3‡	**30th Dec 2020-11th Apr 2021**	5 (17.9)	7 (25.0)	11 (39.3)	3 (10.7)	2 (7.1)
Eased restrictions 3‡	**12th Apr 2021 onwards**	2 (7.1)	6 (21.4)	7 (25.0)	9 (32.1)	4 (14.3)

Values are presented as n (%); † n= 29 as one participant did not answer; ‡ n= 28 as two participants did not answer

Figure 6.3: Impact of the Covid-19 pandemic on self-reported physical activity

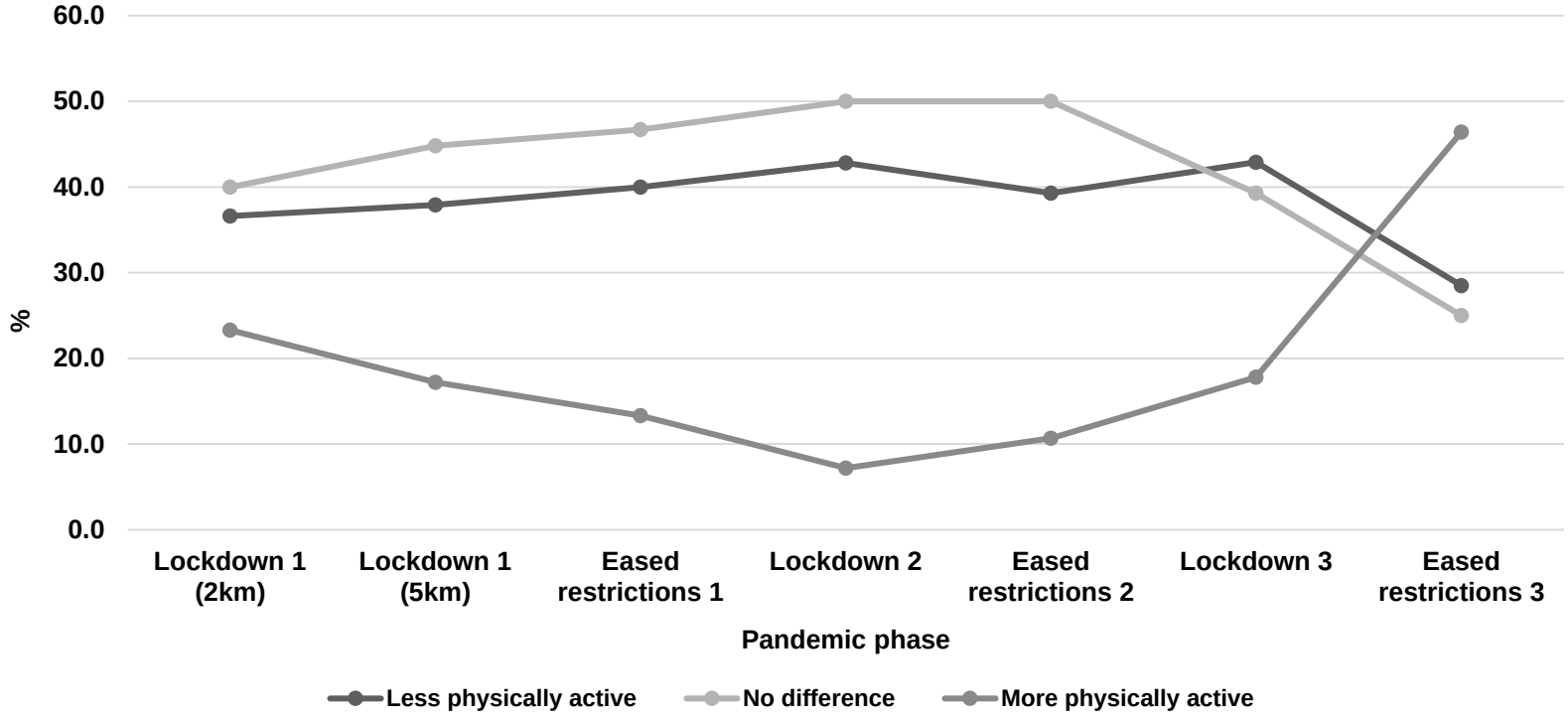


Table 6.7: Impact of lockdown on mobility, functional ability and pain (n= 30)

	A lot less than normal	Somewhat less than normal	No difference	Somewhat more than normal	A lot more than normal
	n (%)	n (%)	n (%)	n (%)	n (%)
Problems with mobility	2 (6.7)	2 (6.7)	20 (66.6)	3 (10.0)	3 (10.0)
Problems with activities of daily living†	3 (10.3)	0	19 (65.5)	7 (24.1)	0
Pain	1 (3.3)	0	17 (56.7)	11 (36.7)	1 (3.3)

Values are presented as n (%); † n= 29 as one participant did not answer

Table 6.8: Concerns regarding physical activity in the next 12-months

Theme	n (%)
Arthropathy	3 (10.0)
Pain	10 (33.3)
Fatigue	1 (3.3)
Fear of Covid-19 transmission	1 (3.3)
Increasing joint mobility	1 (3.3)
Maintaining mobility	1 (3.3)
Increasing physical activity	3 (3.3)
Maintaining physical	3 (3.3)
Access to resources (Gyms)	3 (3.3)
Access to resources (Swimming pools)	4 (13.3)
Access to resources (In-person exercise classes)	1 (3.3)
Dislike of online exercise classes	1 (3.3)
Time constraints	1 (3.3)
Weather	1 (3.3)
Weight gain	1 (3.3)

6.4 Discussion

The aim of this study was to conduct a follow-up assessment of PA in adult PwMSH who participated in the original assessment, and to compare PA between the two time-points. PA awareness and the impact of the Covid-19 pandemic on PA were also assessed. Results revealed no significant differences in objectively measured PA between the two study time-points, although the number of participants who achieved PA guidelines slightly increased at follow-up. PA awareness had also increased in the majority since the original assessment, and a desire to become more active was reported by most. Trends in self-reported PA participation were varied amongst the group throughout the various phases of lockdown and eased restrictions. A variety of reasons for differences in PA were reported, as well as concerns for PA and physical health beyond the third wave of the pandemic.

6.4.1 Physical activity at follow-up

Time spent in all parameters of objectively measured PA were not significantly different in this group of adult PwMSH at follow-up, although the overall achievement of PA guidelines in the group was somewhat higher at follow-up. Since the original assessment, an increased awareness of PA and a desire to become more physically active were reported by the majority of the group. These results are encouraging, and indicate that PA in PwMSH from this study may be increasing amongst some participants. As seen in Study I (Chapter 3), a considerable proportion did not achieve PA guidelines via sustained bouts of MVPA ≥10 minutes. Additionally, some participants demonstrated a regression in PA compared to their original assessment, although the achievement or failure to achieve PA guidelines was not different in the majority. The majority of the group reported they did not know the PA guidelines, and only one participant was able to correctly state these guidelines in full. However, rates of awareness and the ability to somewhat cite the guidelines correctly are in keeping with reports of PA guideline awareness in adults from the general Irish population (Sport Ireland, 2015). Partially cited guidelines suggest an incomplete understanding of what the PA guidelines actually advise, as the emphasis on moderate-vigorous intensity was lacking in the majority of answers; however, a reasonable estimate of the duration of time advised per day or per week was given by most. Overall findings suggest that a small proportion of participants have successfully increased their PA, and whilst the majority appear to have maintained sufficient PA engagement, a considerable number may have regressed or maintained insufficient levels of PA.

In contrast to the results of Chapter 4, where age significantly impacted vigorous PA in older PwMSH, parameters of PA were not impacted by age in the present analysis. Furthermore, self-reported types of PA over the previous year demonstrated that a variety of activities were still undertaken by the group throughout the pandemic. Variation in follow-up time and the smaller sample size at follow-up may limit these findings, although most participants were re-assessed at approximately three years after their initial assessment. Ultimately, the need for interventions and healthcare supports to educate and promote PA in PwMSH appears to have persisted almost three years after the original assessment. Considering participants reported a desire to become more physically active, further

attention and examination of optimal strategies to help PwMSH increase and maintain regular PA are required.

6.4.2 Physical activity during the pandemic

Versloot et al. (2021) reported a decline in sports participation in Dutch adults with haemophilia compared to the general population during the pandemic. Only sports participation was examined by their study, and may have underestimated general PA participation, especially amongst older PwMSH who may be less inclined to engage in sport. The present study, therefore, is the first to demonstrate variations in general PA behaviour in adult PwMSH throughout the various phases of the pandemic.

Although PA appeared to decline for some participants throughout all phases of the pandemic, PA did not change for the majority of participants until the third, longest lockdown. A small proportion of participants increased their PA during the initial lockdown, however PA appeared to return to usual levels or decline further when the 2km radius for exercise was extended to 5km. This trend appeared to continue until the second lockdown restrictions were eased. Contrastingly, a large survey of the Irish general population during the initial Covid-19 restrictions found that the majority of people were more active than usual, with a minority being less active (Forde et al., 2021). Although the majority of PwMSH reported no difference in their PA at the beginning of the pandemic, a considerable amount were less physically active, and only a minority were more active. It would therefore appear that PwMSH may have been less physically active than the general Irish population during the initial restrictions. A proportion of participants had a comorbid history of HIV, therefore medical vulnerability may have contributed to lower PA engagement, or a decreased inclination to become more physically active than usual. Forde et al. (2021) revealed that more time for PA was predictive of being more physically active in the general population during the initial pandemic restrictions. Similarly, a number of PwMSH from this study reported that more time also positively impacted on their ability to be more physically active. Barriers to PA in PwMSH were also similar to those reported by the general population, including a lack of access to usual means of exercise, being advised to stay at home and having to work more than usual. Other reasons for variations in PA during the pandemic included recovering from surgery or injury, and increased parenting demands.

Although mobility, pain and difficulties with activities of daily living were not impacted for the majority during lockdown, 20-40% reported these issues increased, whilst a small proportion reported improvements in these domains. Reports of deteriorating joint health during the pandemic are echoed by Cuesta-Barriuso et al. (2021), who found increased reports of joint pain and reduced joint range of movement in Spanish adults with haemophilia after a period of lockdown, in addition to significant weight gain. The impact of bleeds and haemophilic arthropathy on PA was not feasible to assess in the present study due to limited clinical access, although deteriorating musculoskeletal health, increased pain and potential weight gain may have additionally impacted PA in the present sample. A follow-up assessment of bleeding phenotype, joint health, treatment regimen and body

composition would be interesting to determine potential changes in these parameters since the original research assessment, and examine how they may relate to recent PA levels.

6.4.3 Physical activity beyond the pandemic

A number of concerns for PA within the coming 12 months were reported by the study sample. Pain was the most commonly reported concern, as well as concerns regarding haemophilic arthropathy. Desires to increase or maintain PA were highlighted, as well as the restoration of access to exercise resources, such as gyms and swimming pools. A dislike of online exercise classes and a desire to return to in-person classes were voiced, which reflects the importance of social interaction and support in achieving PA for some. Alternatively, social interaction may deter others from PA engagement in public, particularly for those who are medically vulnerable, and who fear the transmission of Covid-19 variants that continue to circulate in the community. As Ireland continues to emerge from Covid-19 restrictions and many people return to the workplace and busy social lives, pre-pandemic barriers to PA, as outlined in Chapter 5, may also resume for people who have become more active throughout the pandemic. These findings regarding the potential barriers and motivators to PA beyond the peak of the pandemic provide useful insights which may aid the design of personalised interventions to address physical inactivity in PwMSH in the present climate. A variety of PA and exercise intervention options may be required to facilitate various people within the haemophilia community to overcome their own individual barriers to PA beyond the pandemic.

6.4.4 Limitations

A number of limitations in addition to those already discussed should also be acknowledged. The small sample size may have increased the risk of a type II error in statistical analyses, and also may not be fully representative of the target population. The best efforts were made to contact all accessible participants on at least two occasions by leaving voicemails and re-contacting them one week later in the event of non-response; however, the follow-up rate was suboptimal and may have increased the risk of potential non-response bias. Furthermore, during the recruitment period the Irish health-care system experienced a severe cyber-attack. This coincided with an increased incidence of fraudulent phone calls amongst the general Irish population, thus participants may have been less likely to answer their phone to an unknown number. Additionally, observation bias may have impacted the assessment of PA using the ActiGraph accelerometer, especially considering participants were already familiar with the device from the original research assessment; however, it was emphasised to participants to maintain their typical habitual PA during the study period. Lastly, the self-reported nature of the follow-up questionnaire is prone to potential recall bias. Additionally, this questionnaire was designed during the pandemic when access to healthcare professionals and patients was very limited, therefore the potential to validate the questionnaire prior to its dissemination was not feasible within the study timeframe.

6.5 Conclusion

This study demonstrated that objectively measured PA did not significantly change in PwMSH between the original and follow-up assessment time-points. Self-reported PA levels varied throughout the course of the pandemic, but overall PA increased again with the final wave of eased restrictions. An increased awareness of PA and a desire to become more physically active were reported by the majority of participants, therefore interventions to address physical inactivity in PwMSH continue to warrant further exploration in future studies. As Ireland continues to emerge from pandemic restrictions, interventions to address physical inactivity beyond the pandemic should consider individual barriers to PA, including time, pain and access to exercise resources.

Chapter 7: Discussion

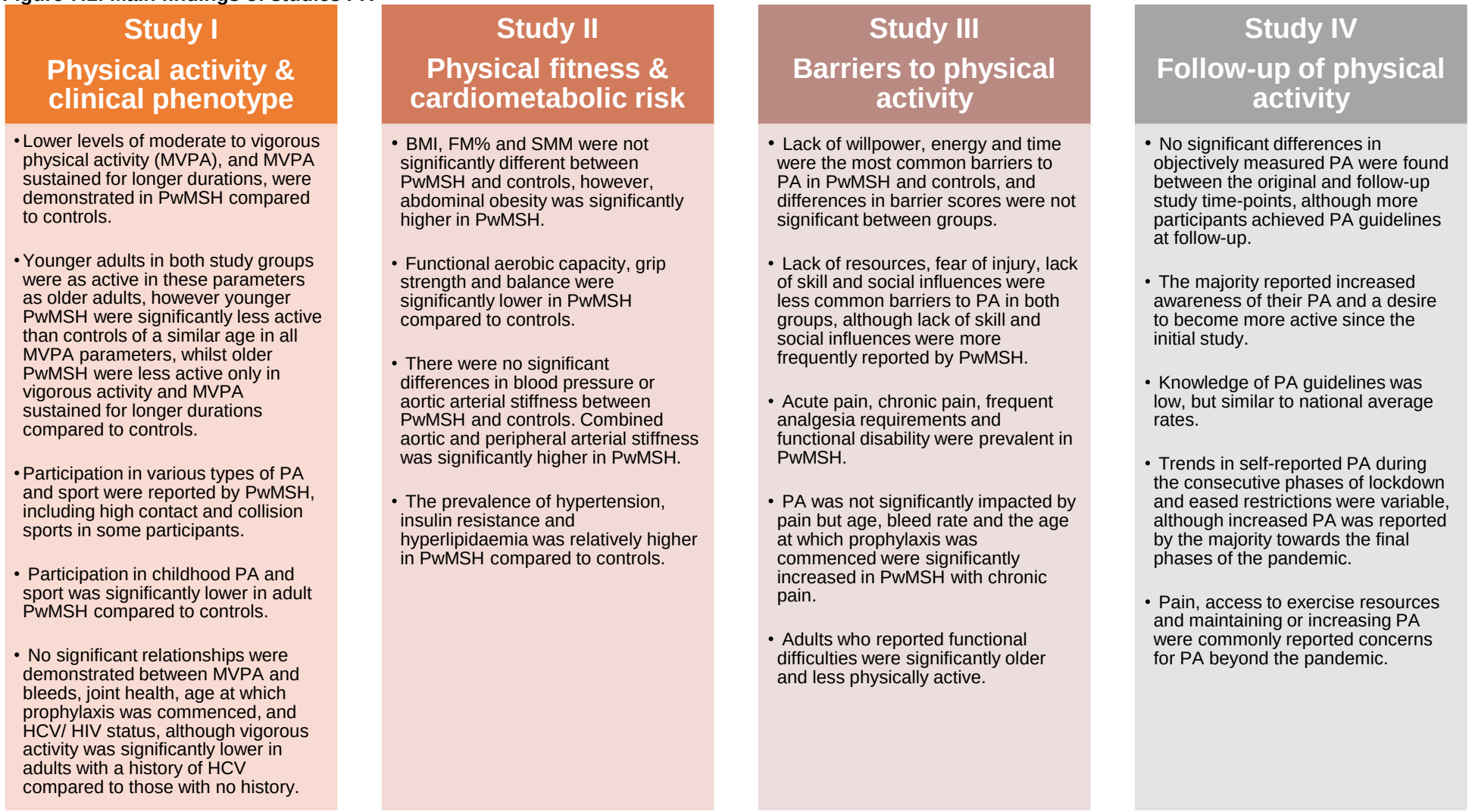
7.1 Introduction

Haemophilia is a bleeding disorder caused by a deficiency in procoagulant Factor VIII or Factor IX, more commonly known as haemophilia A (HA) and B (HB), respectively (Mannucci and Tuddenham, 2001). Disease severity is stratified according to basal clotting factor levels, as severe (<1%), moderate (1-5%) or mild (>5-<40%) haemophilia (Mannucci and Tuddenham, 2001). People with haemophilia (PwH), predominantly those with moderate and severe haemophilia (PwMSH), may experience traumatic or spontaneous bleeding into joints (i.e. haemarthroses) and muscles, resulting in significant pain and functional disability (Mannucci and Tuddenham, 2001). Repetitive haemarthroses in the long-term cause synovitis and osteochondral destruction resulting in chronic haemophilic arthropathy (Raffini and Manno, 2007). Phenotypic variability also exists in PwMSH, as demonstrated by differing rates and severity of bleeding tendency, arthropathy and functional disability (Franchini and Mannucci, 2017). Individuals with a severe bleeding phenotype are typically treated using regular intravenous administration of replacement clotting factor concentrates, in a treatment regimen known as 'prophylaxis', which aims to prevent bleeding and subsequent arthropathy. Factor concentrates were infected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) in the 1980s, which led to significant morbidity and mortality amongst affected PwH (Shapiro and Makris, 2019). The life expectancy of the global haemophilia population has increased in recent decades due to improved haemophilia treatments, as well as treatments that potentially eradicate HCV and suppress HIV; therefore, an increase in age and disease-related comorbidities has been recognised in the haemophilia population (Shapiro and Makris, 2019, Kempton et al., 2021). The World Federation of Hemophilia encourages regular physical activity (PA) in PwH to promote normal neuromuscular development, physical strength, fitness, bone health, function, healthy body weight and positive self-esteem (Srivastava et al., 2020). However, pain and physical disability associated with bleeds and arthropathy present challenges for PwMSH to achieve regular PA, and reap its associated health benefits (Bull et al., 2020). Furthermore, higher intensity PA naturally declines with age (Sallis, 2000), and this may be accelerated in adult PwMSH who have chronic arthropathy and other comorbidities.

The systematic review in Chapter 1 demonstrated variable levels of PA in PwH. The majority of studies assessed PA using only self-reported methods, which are inherently affected by response and recall bias. Furthermore, the relationship between bleeds and PA was difficult to elucidate due to significant heterogeneity in methods and incomplete reporting of bleeding phenotype and treatment regimen. These findings informed the primary aim of Study I, which was to determine PA in adult PwMSH using combined objective and subjective methods. Additional aims were to examine the relationship between PA and age, and PA and clinical phenotypic parameters including bleeds, joint health and treatment regimen. Study II aimed to determine physical fitness and cardiometabolic health risk in PwMSH. Study III thereafter involved an exploration of barriers to PA in PwMSH. Lastly, after a period of postponed research activity due to the Covid-19 pandemic, Study IV aimed to

conduct a follow-up assessment of PA in PwMSH. The impact of the Covid-19 pandemic on PA was also examined. The main findings of Studies I-IV are presented in Figure 7.1.

Figure 7.1: Main findings of studies I-IV



7.2 Collective implications of this research

Physical inactivity is amongst the established leading risk factors for all-cause mortality, as well as several chronic diseases including cardiovascular disease, type 2 diabetes and certain types of cancer (Piercy et al., 2018, Bull et al., 2020, Murray et al., 2020, Katzmarzyk et al., 2022). Numerous health benefits are associated with regular PA, including a reduced risk of hypertension, hyperlipidaemia, weight maintenance, improved bone mineral density, and a reduced risk of falls and related injuries in older adults (Piercy et al., 2018, Bull et al., 2020). There is no doubt that PA has the potential to augment both the physical health and overall well-being across the global population; especially amongst individuals who have chronic health conditions, such as haemophilia.

Overall, this thesis has demonstrated that adult PwMSH participated in lower levels of moderate to vigorous PA (MVPA) compared to similarly aged adults without haemophilia. Evidence of decreased physical fitness and increased cardiometabolic risk were also found. Furthermore, various psychosocial barriers to PA, in addition to chronic pain and functional disability, also impacted a significant proportion of PwMSH. After approximately three years, a follow-up measurement of objective PA in this cohort demonstrated no change in PA for the majority of individuals between the original and follow-up assessment time-points. Fluctuations in self-reported PA were apparent for some throughout the various phases of the Covid-19 pandemic, however ultimately PA increased again for the majority by the third phase of eased restrictions. The need for interventions to promote PA and health was highlighted, as concerns related to PA and physical health beyond the pandemic were reported. The overall findings of this thesis need to be contextualised collectively in relation to each other, in order to inform the most optimal future directions that may stem from this work.

7.2.1 A personalised approach to physical activity

Despite the same diagnosis and similar levels of basal Factor VIII and Factor IX, PwMSH appear to present with a variable multitude of physical health issues which may impact physical functioning and quality of life. This includes disease-specific issues such as bleeds and haemophilic arthropathy, as well as the associated chronic pain and functional disability; however, they also appear to be impacted by general health issues associated with ageing, which may be further augmented due to their haemophilia. This includes being overweight or obese, reduced functional capacity and strength, and impaired balance. Cardiometabolic disorders including hypertension, hyperlipidaemia and insulin resistance were prevalent amongst older adults who also had a comorbid history of HCV or HIV. The historical challenges faced by older adult PwMSH with respect to treatment regimens and iatrogenic infection may evidently have significant implications for physical health and chronic health risk in this cohort. These challenges may not affect younger adults who were not exposed to infected blood products. Differences in attitudes towards various treatment regimens, both existing and novel, should also be considered in this context, and the impact that might have on overall health and quality of life between PwMSH of various ages. Furthermore, the extent of challenges with regard to arthropathy may also differ between younger adults who commenced prophylaxis at an earlier

age, who have relatively limited joint damage, compared to older adults who did not have access to treatment from a young age and have extensive arthropathy. Reduced bone mineral density was also prevalent, which is reflective of the increased risk of osteoporosis in PwH (Petkovic et al., 2022). Personalised prophylactic treatment regimens which encompass an individual's bleeding phenotype, pharmacokinetic profile, musculoskeletal health, PA and lifestyle are suggested to be superior to fixed dosing regimens due to the phenotypic variation which presents with moderate and severe haemophilia (Collins, 2012, Oldenburg, 2015, Von Mackensen et al., 2015). In contrast to the original factors proposed to impact PA in PwMSH at the outset of this thesis (Figure 7.2a), collective findings of this thesis would suggest that a personalised approach to prescribing PA would also be superior to a conventional 'one-size-fits-all' approach, in light of the numerous additional factors which may also impact PA in PwMSH of various ages and generations (Figure 7.2b). Personalised PA and health interventions prescribed for individual PwMSH may optimise the potential to positively impact the various domains of health proposed by the ICF framework (see Chapter 2: Methodology; Figure 2.1) including impaired body functions and structures, activity limitations, participation restrictions, environmental factors, and personal factors.

Figure 7.2a: Original proposal of factors which may impact physical activity in haemophilia

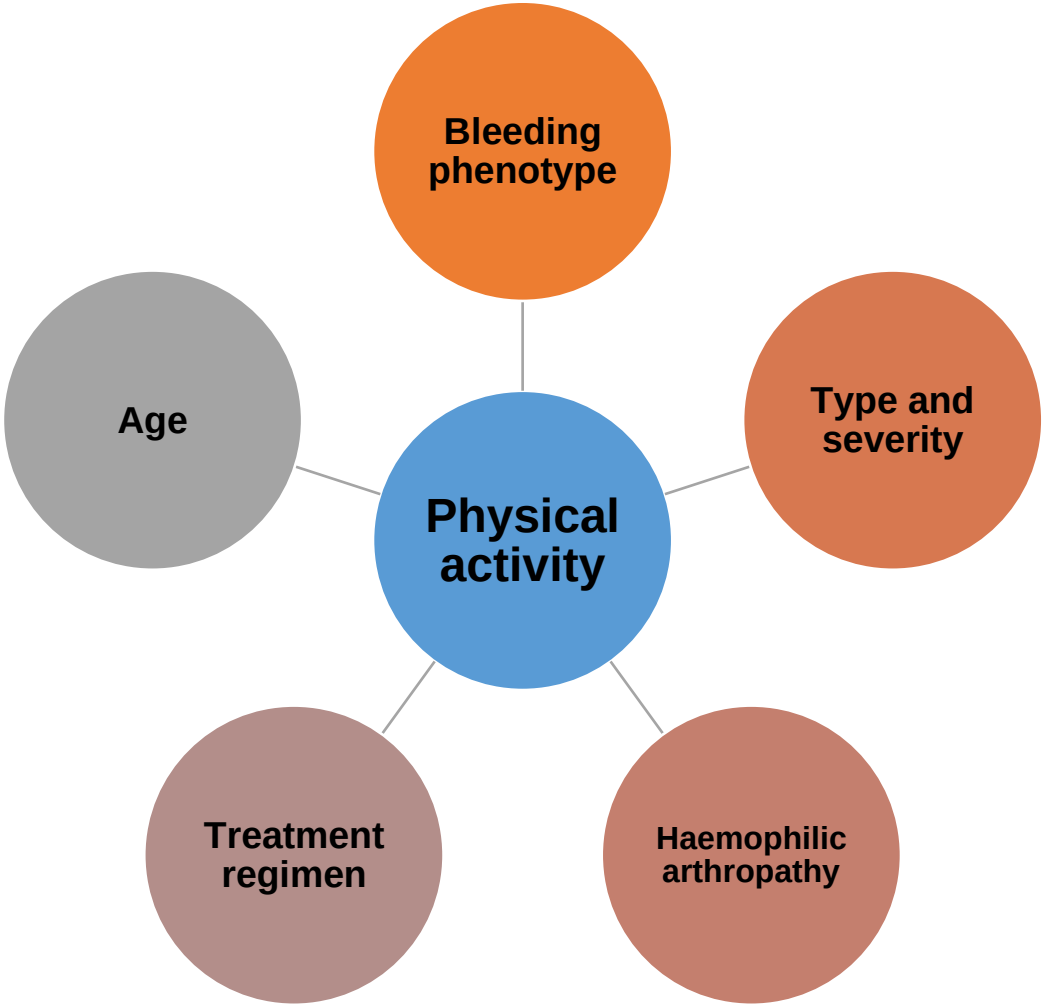
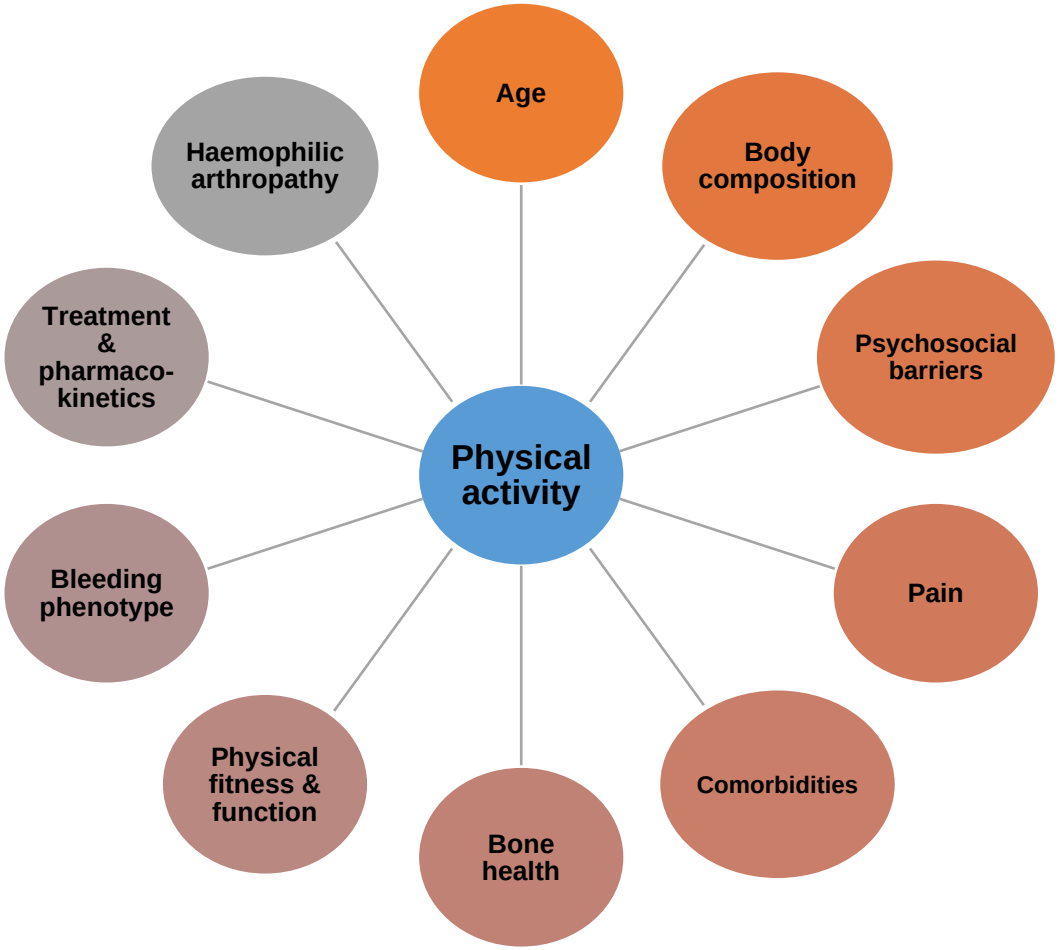


Figure 7.2b: Reformed proposal of factors which may impact physical activity in haemophilia



The most recent PA guidelines advise that adults should achieve 150-300 minutes of moderate intensity PA, or 75-150 minutes of vigorous PA, or some equivalent combination, every week (Bull et al., 2020). In contrast to previous guidelines which advised that PA should be accumulated in bouts of at least ten minutes, the most recent guidelines suggest that higher intensities of PA of any duration are associated with beneficial health outcomes, including reduced all-cause mortality. Furthermore, although more PA is considered to accumulate more health benefits, PA beyond these thresholds does not necessarily appear to reap any additional health benefits (Bull et al., 2020). For individuals not meeting guidelines or for those with chronic conditions, it is further recommended that even some PA will bring benefits to health, therefore individuals should aim to engage in as much PA as possible according to their abilities (Bull et al., 2020). Although the optimal duration and intensity of PA advised by the guidelines adopts a 'one-size-fits-all' approach for promoting regular PA participation in the general population, the fact that relative health benefits may be achieved with even light PA in individuals who cannot achieve these guidelines is very encouraging.

There was a history of significant arthropathy in this cohort of PwMSH who were predominantly treated with either secondary or tertiary prophylaxis. Study I highlighted that although the overall duration of MVPA achieved by the group was significantly lower than that of controls, encouragingly, the majority actually did achieve at least 150 minutes of moderate PA per week (72.9%). This is particularly positive in light of the national male average rate reported to achieve PA guidelines (54.0%) (Healthy Ireland, 2019), although differences in assessment methods of PA may affect this interpretation. Notably, although the majority achieved PA guidelines, findings of Study II were not reflective of the associated health benefits of PA in light of the higher relative rates of abdominal obesity, hypertension, hyperlipidaemia and insulin resistance identified in PwMSH compared to adults without haemophilia. Affected participants were also less physically fit compared to controls, as demonstrated by the significantly lower functional aerobic capacity, strength and higher levels of balance impairment amongst the group. Furthermore, the findings revealed by Study III suggested that PwMSH may experience potentially heightened barriers to PA, including numerous psychosocial barriers, as well as pain and functional disability in comparison to adults without haemophilia. To demonstrate the variation in phenotypic presentation, multi-morbidity and barriers to PA adult PwMSH may present with, two fictitious case reports are described below:

Case 1

A 58-year old man who has a history of severe HA. He was commenced on tertiary prophylaxis at the age of 24. Adherence to his prophylaxis regimen has been limited over many years as he has a rapid factor half-life clearance, difficult venous access and does not like self-administering frequent injections. His wife helps him with this, even though she finds it challenging. He experienced one traumatic bleed to his forearm and three spontaneous ankle bleeds in the past year. He has no history of inhibitors, but he suffers with chronic haemophilic arthropathy with a Haemophilia Joint Health Score (HJHS) of 42, particularly affecting his right ankle and left elbow, which are both significantly restricted. Arthropathy has caused him significant chronic pain for as long as he can

remember. He successfully underwent treatment for HCV and has achieved a sustained viral response, however he currently takes antiviral medication for the management of HIV. He has a waist circumference of 102 cm and a BMI of 31.0 kg/m^2. He has hypertension, type 2 diabetes, hyperlipidaemia and osteoporosis, which are all being treated with medication. Unfortunately, treating his chronic pain pharmacologically has been relatively limited in light of his comorbidities and age, and he is currently seeking an orthopaedic opinion to treat his chronic ankle arthropathy. Walking very long distances is difficult to tolerate in light of the pain associated with his arthropathy, but he tries to get out for short walks everyday with his wife in their local park. She is protective of him and does not like him to over-exert. He would love to be able to walk the length of the beach someday, but feels this is currently beyond his potential due to his numerous health issues.

Case 2

A 35-year old man who has severe HB. He was commenced on prophylaxis at the age of 10. He has no history of inhibitors but his HJHS is 15, with significant arthropathy predominantly affecting his left ankle. He has had no bleeds over the past year and is very adherent to his treatment regimen. He has no known comorbidities, although his most recent bone health scan showed evidence of osteopenia. He tries to keep active by cycling to and from work, but finds it difficult to fit in any additional PA as he works in a highly demanding corporate job, and his wife has just recently had a baby. His ankles have been causing him more pain than usual recently, so he has been prescribed Arcoxia. He has a waist circumference of 95 cm and a BMI of 26.5 kg/m^2. His most recent blood pressure readings have been in the high-normal range and his doctor has advised him to adapt his lifestyle to try and bring these readings down. He feels stressed in light of these new health concerns, especially considering he is the sole breadwinner at home and his work is very demanding. He wants to act now to improve his health and prevent these issues worsening over years to come.

Evidently, it may be unrealistic to expect PwMSH, who are potentially burdened with multi-morbidity and multiple barriers to PA, to achieve much more beyond the lower guideline threshold of 150 minutes of moderate intensity PA per week. Additionally, the general guidelines as they stand may be beyond the grasp of certain individuals who are significantly burdened with joint disease and other potential comorbidities. In light of recent evidence which has proposed that light intensity PA is in fact associated with improvements in cardiometabolic risk and all-cause mortality (Chastin et al., 2019), even minimal to modest increases in PA may bring some relative health benefits to those who are not able to achieve moderate to vigorous levels of PA. Case 1 and Case 2 presented above present with differing levels and severity of multi-morbidity relative to their age. Both appear to be as physically active as they can be in light of the significant challenges they face with their health, as well as multifaceted barriers to PA which may potentially exacerbate these health issues. Certainly, their goals for PA differ at this point in their lives. Different lifestyle adaptations and levels of multi-disciplinary input would be required to facilitate their goals to improve their overall health and quality of life. It is further evident that the same PA programme and goals for PA cannot be applied to both cases, highlighting the importance of a more personalised approach to PA. Ultimately, a personalised

approach to PA may be more effective in bringing about significant and meaningful improvements to health and quality of life in PwMSH.

7.2.2 Considerations for physical activity to improve health

Although the majority of PwMSH in Study I achieved minimum PA guidelines, MVPA achieved in sustained bouts of at least ten minutes (i.e. Freedson bouts) was significantly lower compared to controls, suggesting a lower exercise tolerance in PwMSH. Certainly, physical fitness can be improved with specific exercise training, including aerobic training to improve cardiorespiratory fitness, resistance training to improve muscular strength or endurance, and proprioceptive training to improve balance (Pollock et al., 1998, Garber et al., 2011, Riebe et al., 2018). The overload principle underlies the associated dose-response relationship that exists between exercise and the training effect, whereby a low training stimulus will result in a low training effect, and a high training stimulus will result in a greater training effect (Pollock et al., 1998). Consequently, the magnitude of benefits to be obtained from PA is influenced by the volume and intensity of activity. It is therefore plausible to assume that limitations in exercise tolerance may influence the magnitude of health benefits that may be achieved via PA in various PwMSH. In light of the clinical phenotypic variation PwMSH may present with, reasons for limited exercise tolerance may also be variable and multi-faceted. Tolerance may be potentially influenced by the bleeding phenotype and the extent of haemophilic arthropathy, pain and physical disability experienced by an individual. The consideration of treatment regimen influences such as type of factor product and product half-life clearance also warrant consideration. Additionally, tolerance may be limited by increased body weight, reduced skeletal muscle mass, comorbid health issues and intrapersonal barriers to PA, such as fear of bleeds or joint injury and fatigue.

Study II demonstrated a lack of association between PA guideline achievement and multiple physical fitness and cardiometabolic risk parameters. This would suggest that PA or exercise alone may not be sufficient to improve overall health outcomes and chronic disease risk in PwMSH. Furthermore, Study IV revealed that although PA appeared to fluctuate for some participants throughout the course of the pandemic, PA was not significantly different in the majority of the group between the original and follow-up assessment time-points. Therefore, it could be assumed that differences in these health outcomes may not have changed, or may have potentially worsened in the interim study period. Unfortunately, it was not feasible to re-assess these health outcomes in Study IV, however a follow-up assessment would be beneficial beyond this thesis. Regardless, the role of PA and exercise in the treatment and management of multi-morbidity needs to be thoughtfully considered.

There is an abundance of reviews and studies on the effects of various modalities of exercise in the haemophilia population, including resistance, aquatic, aerobic and proprioceptive training, all which have demonstrated improvements in joint range of movement, strength, aerobic fitness, balance and pain amongst heterogeneous samples of PwH (Siqueira et al., 2019). There is a lack of studies which have investigated the effects of exercise or PA on cardiometabolic risk parameters in PwH. Parhampour et al. reported favourable effects of combined resistance and aerobic exercise training

over resistance or aerobic training alone for reducing harmful blood lipids and waist circumference in people with moderate HA (Parhampour et al., 2019, Parhampour et al., 2021). Considering exercise has the potential to favourably impact multiple health outcomes simultaneously, future studies in PwH should personalise exercise interventions designed to impact personalised health outcomes depending on the extent of potential multi-morbidity they present with. This may include reduced fitness, impaired function, increased adiposity, poor bone mineral density or various comorbidities, as outlined in Figure 7.2b.

In light of the limited exercise tolerance in PwMSH demonstrated in Study I, one particular modality of exercise training which has not been explored to date in this population is interval training. High intensity interval training has been reported to be safe, well-tolerated and feasible in people with rheumatoid arthritis and osteoarthritis, resulting in improved cardiorespiratory fitness, muscular strength and disease activity (Bartlett et al., 2018, Golightly et al., 2021). It has also been associated with improvements in cardiometabolic risk factors including body composition, blood pressure and insulin resistance (Batacan et al., 2017, Campbell et al., 2019). Certainly, the prospects for some PwMSH to achieve a vigorous, high-intensity threshold with this type of training may evidently be limited, therefore the exploration of low and moderate intensity interval training programmes would be of interest in this population. Interestingly, equivalent or stronger associations have been identified between light intensity PA with cardiovascular disease markers compared to moderate intensity PA in people with rheumatoid arthritis (Khoja et al., 2016, Hammam et al., 2019). Furthermore, a Cochrane review explored the effects of high versus low intensity training programmes in people with osteoarthritis (Regnaux et al., 2015). In light of the few studies of low quality included in the review, authors concluded further studies are required to determine the optimal dose-response relationship between exercise and clinical outcomes, particularly the minimal threshold required for a clinically meaningful effect and the maximum threshold that can be safely tolerated. However, considering individual benefits may be relative in response to exercise of various intensities, personalised approaches to the implementation of such exercise interventions may be worth exploring compared to a one-size-fits-all exercise programme.

A similar principle may be applied to resistance training programmes considering light intensity resistance programmes have been shown to safely increase strength in PwH without adverse events (Wagner et al., 2020). Resistance training itself is also associated with reduced cardiometabolic risk (Ashton et al., 2020). Study II demonstrated PwMSH had lower grip strength and impaired balance compared to controls. Reduced bone mineral density was also prevalent in a significant proportion of the group. Therefore, the incorporation of resistance and proprioceptive training would be particularly important in older PwMSH in light of the increased risk of potential frailty and falls with age. A recent review reported an increased risk of falls and fracture in PwH compared to the general population (Petkovic et al., 2022). Impaired balance, mobility, gait, weakness and orthopaedic status were factors associated with falls in PwH.

Notably, the literature to date generally places more emphasis on the impact of lower limb arthropathy on physical functioning in adults with haemophilia. The ankle tends to be the most severely affected

joint in most PwMSH, therefore its impact on lower limb strength, balance and gait is certainly concerning; however, the second most severely affected joint according to the HJHS was the elbow. Grip strength was correlated with individual HJHS of the elbow and upper limb skeletal muscle mass in Study II. Therefore, the functional implications of upper limb arthropathy should not be neglected, especially in ageing PwMSH. Sufficient upper limb function is paramount for independently undertaking personal activities of daily living such as brushing teeth, grooming, washing and dressing. Additionally, the majority of participants in Study IIIb, who were older, reported experiencing difficulties with ADLs. Evidently, the impact of upper limb arthropathy on daily functional tasks warrants further exploration beyond this thesis. Personalised exercise programmes aimed at preserving and improving upper limb function may be critical for maintaining independence and optimising quality of life in ageing PwMSH.

Improvements in chronic disease risk are associated with even modest weight loss (Goldstein, 1992, Klein et al., 2004, NICE, 2006). Furthermore, weight loss using a combination of diet, exercise and behaviour modification has also been shown to reduce pain, functional impairment and inflammatory markers in other disease populations, including people with rheumatoid arthritis (Janke et al., 2007, Gleeson et al., 2011, Somers et al., 2022). Achievement of the PA guidelines in Study II via total MVPA and MVPA achieved via sustained Freedson bouts significantly influenced certain body composition parameters in the control group; however, body composition was not significantly altered by PA status in PwMSH. PA is considered to play more of an adjunct role in the process of weight loss, which is predominantly mediated by diet (Shaw et al., 2006), although regular PA has been shown to be important for maintaining achieved weight loss (Johns et al., 2014). Reports of combined diet and exercise have also been reported to be superior to diet or exercise alone (Curioni and Lourenço, 2005, Dombrowski et al., 2014, Twells et al., 2021). The role of PA in augmenting weight loss programmes in PwMSH may however, be limited in light of the evidence of low exercise tolerance in this group. High volumes of more intense PA are suggested to be required in order to substantially contribute towards effective weight loss (Donnelly et al., 2009, Cox, 2017), therefore interventions which place more emphasis on diet and nutritional intake may have more potential to improve health outcomes in overweight or obese PwMSH. Specialised input from dieticians and nutritionists would be paramount to achieving effective weight loss, especially for certain PwMSH who have comorbidities such as type 2 diabetes. A survey of obese patients with haemophilia in the United States demonstrated that patients were aware of the general and haemophilia-specific consequences of excess body weight. However, due to a lack of successful weight loss, a desire for more education and specific advice on weight management was voiced by participants and their caregivers (Croteau et al., 2020). A similar survey in the Irish haemophilia population would be useful in order to determine the extent of body weight awareness and to inform the design of personalised weight loss interventions.

Evidently, there is a wealth of potential for exercise and PA to improve a multitude of targeted health outcomes in PwMSH. Interventions should be tailored to the individual and specialised multi-disciplinary input may also be required in addition to PA. Furthermore, personalised PA should also

consider that the same level of intervention may not be required by every individual. Various options and levels of support may be required, depending on the extent of potential multi-morbidity and barriers to PA individual PwMSH may present with.

7.2.3 Optimising a personalised approach to physical activity

In order to successfully implement a personalised approach to PA and health in PwMSH, many factors warrant consideration in the design of such an intervention. Qualitative information provided throughout the studies of this thesis has provided important insights to the barriers to PA that PwMSH may encounter. The consideration of barriers to PA would be paramount to the design of personalised PA programmes, in order to help individuals to overcome barriers and successfully participate in the respective intervention.

Barriers common to everyday life present challenges in achieving regular PA amongst the general population, including a lack of time, energy and motivation for PA (Seefeldt et al., 2002, Spiteri et al., 2019). Study IIIa highlighted that these were also the most commonly reported barriers to PA in PwMSH, no differently to adults without haemophilia. However, it is important to acknowledge that the Barriers to Being Active questionnaire was limited in its ability to provide further depth of explanation for these barriers in study participants. In light of the clinical phenotypic presentation of haemophilia, it would be satisfactory to assume that the factors which influence these common barriers to PA may be different for PwMSH compared to the general population. A lack of willpower, energy and time may be driven by the additional burden of haemophilia in different individuals. For instance, additional time is required to take prophylactic treatment. Some individuals may need to administer prophylactic treatment on more than one occasion per week, depending on individual pharmacokinetics and the type of treatment product they are using. This may be particularly challenging for those who are fearful of self-treatment and for those with difficult venous access. Furthermore, pain and fatigue associated with chronic arthropathy and impaired physical function may influence lack of willpower and lack of energy. Comorbidities may further influence fatigue in some individuals which was not comprehensively assessed in this project, but warrants further exploration. Fatigue may particularly impact PwMSH who have a history of HCV, as liver cirrhosis and side effects of older HCV treatments are associated with increased fatigue in the general HCV population (Sarkar et al., 2012). Fatigue is also highly prevalent in individuals with HIV due to a myriad of physiological and psychological factors (Xiao et al., 2020).

The potential influence of family and significant others on PA behaviour is an important finding of this thesis. Study IIIa revealed that a lack of skill and social influences were more frequently reported in PwMSH compared to controls. Furthermore, Study I demonstrated that PA participation during childhood was significantly lower in PwMSH compared to controls. PwMSH were not encouraged or given permission in some cases to participate in PA due to the risk of bleeds and joint damage. This may have been due to less optimal treatment options available to older adults in particular when they were younger. Family and care provider influences have been reported to strongly influence childhood PA behaviour (Hesketh et al., 2017). Understandably, protective instincts of parents and

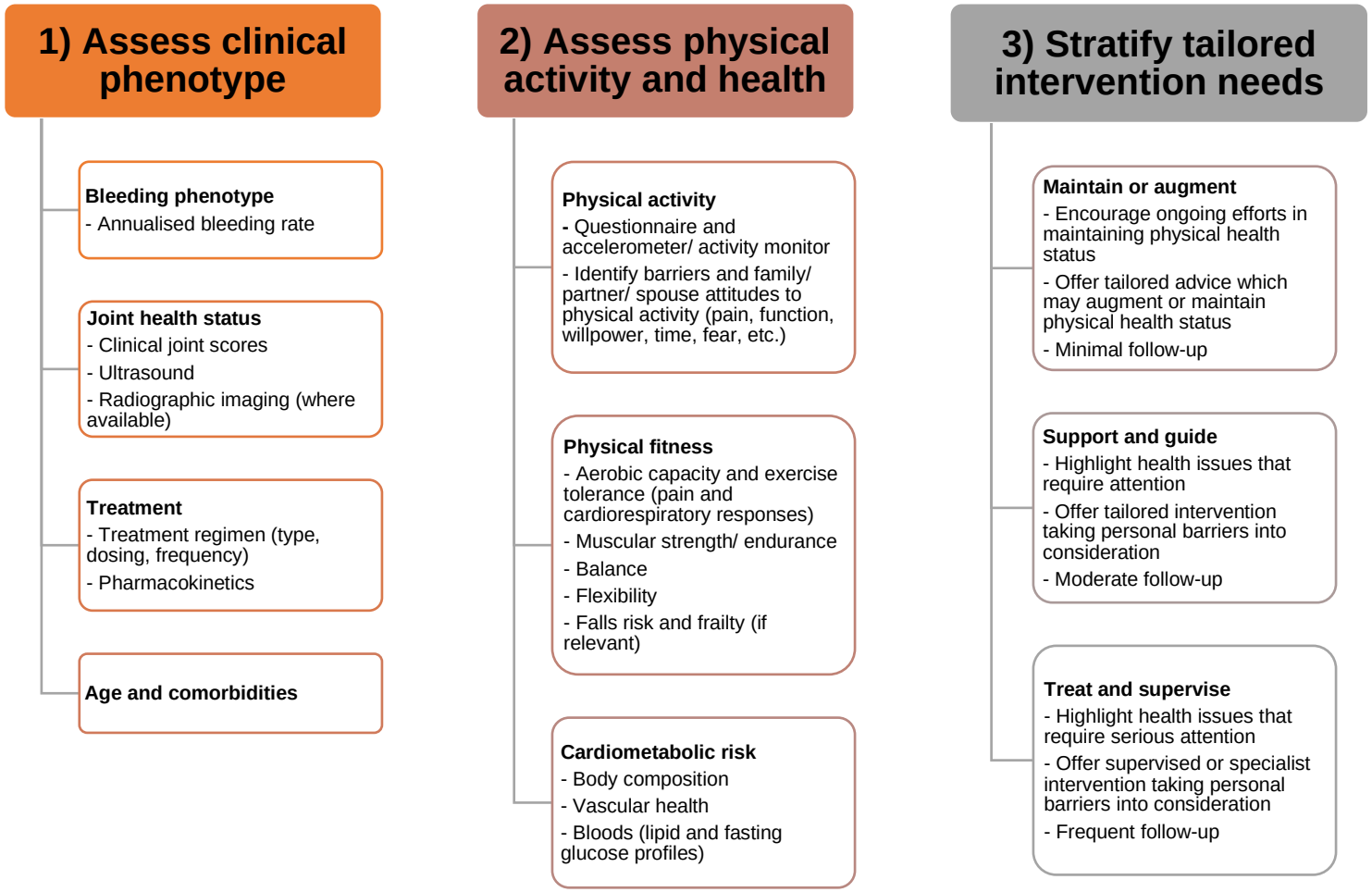
care-providers may have influenced PA participation in PwMSH during childhood, therefore such influences may continue to impact PA into adulthood. The involvement of family members has been suggested to be critical for sustained behaviour change (Guagliano et al., 2020). Studies have examined family-based PA interventions for increasing PA in children, which have been found to be feasible and effective in increasing family PA participation (Brown et al., 2016, Guagliano et al., 2020). It may therefore be interesting to involve family members and significant others in future interventions designed to address physical inactivity in PwMSH. Qualitative studies exploring the beliefs and attitudes of family members and loved ones affected by haemophilia would also be useful for exploring the feasibility of such interventions, as well as barriers or facilitators to PA in PwH from their perspective. This would also be interesting to compare with a paediatric population, who will have grown up with more access to modern day haemophilia treatments.

Study IV revealed that certain issues such as pain and physical functioning deteriorated during the pandemic for some PwMSH. Furthermore, pain, access to exercise resources and maintaining or increasing PA were raised as concerns for PA beyond the pandemic. As Ireland has emerged from the pandemic, access to gyms and swimming pools has been restored which has hopefully had a positive impact on PA for PwMSH who use these facilities for exercise. However, new Covid-19 variants continue to circulate amongst the community during the present time, therefore medically vulnerable individuals who are at an increased risk of severe infection, may be less inclined to use public exercise resources. Insights from the study by O'Donovan et al. (2020) may be useful for informing remote PA interventions which could be delivered using telehealth or e-health in the Irish haemophilia population, which may better suit certain individuals in the post-pandemic era. The authors reported improved attendance to multi-disciplinary outpatient consultations and a sense of improved access to services amongst patients. Interest in remote exercise classes or the use of other online exercise resources was also voiced amongst a proportion of PwH, which highlights the future potential for online technology to enhance PA and health in this population. Furthermore, the target population size of haemophilia in Ireland is relatively small compared to the national population of Ireland, and many people may be sparsely populated around the country. As of 2020, the estimated number of people with moderate or severe haemophilia of all ages under the care of a haemophilia treatment centre was 329 [Moderate: HA (46)/ HB (21); Severe: HA (212)/ HB (50)] (WFH, 2020). This may limit the potential for regular access to in-person multi-disciplinary health services and interventions for many. Telehealth and e-health applications to personalised PA and lifestyle programmes therefore may offer innovative strategies to optimise access to such services amongst the haemophilia population. This warrants further investigation beyond this thesis.

A personalised approach to PA and health in PwMSH warrants a thorough assessment of PA, physical health outcomes and barriers to PA. Health profile, barriers to PA and the level of intervention required amongst individuals may vary, as the findings of this thesis would suggest. Therefore, stratifying individuals based on personalised needs and goals for PA and health may be more beneficial than offering generic exercise advice to all PwMSH. In addition to outcome data collection of bleeding phenotype, joint health, treatment regimen parameters and pharmacokinetic

indices, the assessment may include a baseline assessment of PA and exercise participation, body composition, vascular health, pain, physical fitness and potentially frailty parameters in older adults. Individuals could then be stratified based off their assessment findings, according to the level of intervention they may require. This may range from advice about maintaining or potentially augmenting current physical health status where a person is already quite active and presents with no major health concerns, to higher levels of intervention with specialist multi-disciplinary input for those who have difficulty in achieving PA and are potentially burdened with multi-morbidity. Additionally, from a perspective of the various treatment options available and the ongoing development of novel therapies for PwMSH in the present day, the impact of personalised treatment regimens on PA and physical health outcomes should also be considered. This proposed care pathway for a personalised approach to PA and health in PwMSH is presented in Figure 7.3.

Figure 7.3: A personalised approach to physical activity and health in haemophilia



7.3 Critical analysis of this work

Certain aspects of this research project were inherently limited due to a number of factors which warrant acknowledgement and further explanation.

7.3.1 Study design and sampling approach

The systematic review in Chapter 1 identified the need for more objective measurements of PA and more robust reporting of bleeding phenotype and treatment regimen in studies of PwH. It was also evident that a prospective, longitudinal study design would be superior to determine the relationship between physical activity and bleeds. However, such a study design was simply not feasible to design and conduct effectively within the timeframe of this PhD. Therefore, a cross-sectional study design was used to determine PA using combined objective and subjective methods, as well as to examine the relationship between PA and clinical phenotype. Cross-sectional studies are limited in their ability to infer temporality or causation between variables, however findings of this research have certainly informed a number of potential areas for further investigation in future studies.

Furthermore, convenience sampling was used to recruit participants for this project. Randomised sampling was not feasible considering haemophilia is a rare genetic disorder, and the Irish male population with moderate and severe HA and HB is relatively small compared to the national population of Ireland. The estimated target population of people with moderate and severe HA and HB of any age under the care of a haemophilia treatment centre in 2017 when this PhD commenced was approximately 330 people [Moderate: HA (38)/ HB (25); Severe: HA (209)/ HB (58)] (WFH, 2017). Of the overall target population, 208 adults with moderate and severe haemophilia were registered at the National Coagulation Centre in 2017. In light of the small target sample, randomised sampling may have negatively impacted recruitment for this project, therefore convenience sampling presented the best possible opportunity to obtain a representative sample of the adult target population. Convenience sampling was also used to recruit controls from the staff and student population of St. James's Hospital, Tallaght University Hospital and Trinity College Dublin. This was largely due to the ease of access to recruit potential study participants. Furthermore, the potential to recruit controls from the greater general population outside of these settings was not feasible within the timeframe and resources available to conduct this research. The main limitation with this sampling approach was the potential introduction of selection bias.

7.3.2 Sample and recruitment

It must be acknowledged that the sample recruited may not be fully representative of the overall target population due to potential selection bias introduced by the convenience sampling approach. Information about non-responders could not be ascertained, therefore potential non-response bias could not be measured. The grouping of all types and severity of haemophilia for analysis may also have impacted results due to the inter-individual variation known to exist in the clinical phenotype of moderate and severe haemophilia, and HA compared to HB, however this is a common limitation of

haemophilia research due to the limited sample sizes that are generally recruited. Furthermore, people with mild haemophilia and female carriers of haemophilia were not eligible for recruitment within the scope of the iPATH study, therefore the external validity of the findings of this thesis may only be applied to males with moderate and severe haemophilia. Similar research in these groups of people warrants further exploration in future studies to ascertain PA and physical health outcomes relative to PwMSH.

The target population size of the control group was unknown as the total number of staff and students across the three recruitment sites could not be ascertained. Similar to participants with haemophilia, potential non-response and selection bias must be acknowledged due to a lack of information about non-responders and the sampling approach used, respectively. Compared to the national reported prevalence of PA participation, being overweight or obese and cardiometabolic disorders (hypertension, hyperlipidaemia and insulin resistance) (Healthy Ireland, 2015, Healthy Ireland, 2019), it would appear that the majority of the control group may have been potentially healthier and more active than the greater general population. Furthermore, the fact that they were recruited predominantly from a healthcare setting may also have meant they were a generally more health conscious group.

A number of factors beyond control may have impacted overall recruitment for this project. The Covid-19 pandemic prevented further data collection of already scheduled study participants and ultimately disrupted any further recruitment. Prior to this, the introduction of the General Data Protection Regulation in 2018 also resulted in postponement of further recruitment and data collection due to extended waiting times for ethical approval of updated GDPR compliant study documentation.

7.3.3 Outcome measures

A number of self-reported outcome measures were used throughout this project which may have increased the risk of response or recall bias in the results, particularly the use of retrospective questionnaires amongst all studies, including the Modifiable Activity Questionnaire which was used to obtain information on the types of PA study participants undertook. Furthermore, the Barriers to Being Active questionnaire is not specific to haemophilia or formally validated in this population. Additionally, the PROBE questionnaire which was used to examine pain and functional disability in PwMSH did not provide specific details regarding the intensity of pain or the extent of functional disability in study participants, or the complex multi-faceted aspects to these constructs in PwMSH. Therefore, the representation of barriers to PA, pain and functional disability has inherent limitation.

There was a lack of alternative superior measures that would be feasible to address certain outcomes such as the ABR and the age at which prophylaxis was commenced, which may also be influenced by response and recall bias. Additionally, the study period of the ABR measurement varied amongst participants. Variation in treatment products and the length of time on new products (i.e. the switchover from standard half-life to extended half-life products) also may have impacted the ABR

measurement. The interpretation of joint health in this group of PwMSH may have been impacted by the limited validity of the HJHS in adults, however alternative superior methods to determine joint health were not available for this study. Although the most recent HJHS was used for all participants, the HJHS was assessed at different time-points to the participant's PA and health assessment, which may impact the interpretation of results examining the relationship of these variables. Furthermore, there was missing data for the HJHS in the majority of participants with moderate haemophilia which was beyond control, therefore the representation of joint health is predominantly reflective of the severe haemophilia population only.

The selection of physical fitness measures used in Study II was limited by a lack of extensive validation studies in the adult haemophilia population. The use of the 6MWT as an indicator of cardiorespiratory capacity and fitness was therefore inherently limited, however this test was chosen in order to provide some indication of aerobic capacity in this group. It was also considered important not to choose exercise tests that would put participants at a risk of bleeds or joint injury, especially considering PA was to be assessed across the subsequent week amongst the participants. The potential to conduct a pilot study using a more objective measure of physical fitness in a small subset of participants was ultimately not feasible due to the pandemic, but may be revisited now that Ireland has emerged from Covid-19 restrictions.

The ActiGraph accelerometer provided the most objective measurement of PA available for this project, although it is not without limitation. Although it was emphasised to participants to try and maintain a typical week of PA, they may have been influenced by the Hawthorne effect. Furthermore, the ActiGraph is unable to detect the intensity of certain types of activity undertaken in water or which involve a static trunk posture such as swimming or cycling, potentially underestimating these types of PA. The recruitment and data collection time period varied amongst study participants, therefore seasonal fluctuations may have impacted results. The analysis of the relationship between objectively measured PA and clinical phenotypic parameters such as the ABR and HJHS was only based on one week of PA, which evidently has inherent limitation.

7.3.4 Statistical analysis and missing data

The risk of a type II error in statistical analysis must be acknowledged in light of the limited sample size. Despite the best efforts to obtain full datasets, some data were missing due to a number of reasons. Some participants were not able to complete the full research assessment due to a lack of time on the day on their part, or a lack of ability to complete the research assessment due to incidental high blood pressure readings on the day (>140/90 mmHg). Appropriate medical follow-up was arranged for these participants. Furthermore, a number of returned questionnaires were returned uncompleted in parts. Lastly, the grip strength dynamometer and the Mobil-O-Graph blood pressure monitor for the assessment of vascular health were not available on the day of assessment for a number of participants as the equipment had been sent away for servicing without the researcher being informed. Unfortunately, this was beyond the researcher's control.

7.4 Future directions of this research

Upon reflection of the findings and limitations of this work, a number of future directions warrant further exploration beyond this thesis:

- From Study I, the relationship between PA and bleeds, arthropathy and the age at which prophylaxis was commenced appeared to be very weak. A more detailed analysis of the relationship between various types of treatment on PA and bleeds was not possible due to the limited sample size (i.e. on demand vs. prophylaxis; extended half-life products vs. standard half-life products vs. non-factor products). Furthermore, a cross-sectional study design limited the ability to determine any causative inference between PA and clinical phenotypic parameters. Although it was possible to conduct a remote follow-up of PA in study participants for Study IV, it was not feasible to obtain follow-up data for the Annualised Bleeding Rate and the Haemophilia Joint Health Score. Ultimately, the relationship between PA and bleeds, treatment regimen and haemophilic arthropathy warrants further investigation in large prospective, longitudinal cohort studies. The rapidly evolving treatment landscape of haemophilia should also be considered in this context, by comparing the influences of novel therapies, as well as the differences between various age groups and stages of treatment commencement. The use of modern technology may enhance the prospective measurement and real-time data collection of PA, bleeds and treatment parameters via the use of commercial fitness trackers and smartphone apps. International collaboration may be beneficial for such a study design in order to expand the target population and recruit a sufficient number of participants to achieve sufficient statistical power. The feasibility of such a study should be explored initially to determine enrolment potential, as well as important considerations from a patient and healthcare provider perspective for the design of the study.
- From Study II, the battery of physical fitness tests selected to obtain estimates of aerobic capacity and general body strength provided limited information on the extent of reduced physical fitness in PwMSH. Therefore, a more thorough assessment of physical fitness in adults with haemophilia is recommended. Furthermore, there is evidently a scarcity of validated physical fitness tests in adults with haemophilia. The validity of physical fitness tests therefore warrants further investigation. It should be considered that the tolerance of testing may be limited by pain, joint range of movement, potential muscular atrophy, the presence of comorbidities and fear avoidance in certain PwMSH with extensive joint disease, therefore it would be prudent to carefully consider the duration and magnitude of exertion required by various fitness tests. A pilot study to determine the feasibility of a number of different types of fitness test to assess cardiorespiratory fitness, muscular strength and endurance, balance and flexibility with testing conducted on different days over time, may be a safer and more practical means of conducting such a study. Furthermore, pain was not significantly related to PA in Study IIIb, therefore the concurrent measurement of pain during

physical fitness testing could provide further insights of the complex relationship between pain, exercise tolerance and PA.

- From Study II, the equipment used to measure arterial stiffness provided an estimate of this variable using a brachial cuff monitor. The gold standard clinical measurement of arterial stiffness involves the assessment of carotid-femoral pulse wave velocity (Segers et al., 2020). In light of the inverse trend demonstrated between peripheral arterial stiffness, measured using the augmentation index, and age, as well as the joint score and age at which prophylaxis was commenced, this relationship warrants further exploration using more robust methods of arterial stiffness and more objective measurements of joint health (e.g. ultrasound or radiographic joint imaging). Consultation with professionals who are experts in the measurement of these variables would be required in such a study.
- From Study III, the Barriers to Being Active questionnaire provided a broad sense of the types of barriers to PA that affect PwMSH, however it was not specific to haemophilia, or formally validated in the population. Furthermore, the use of the PROBE questionnaire to examine pain and functional disability had inherent limitation, as discussed. Further depth and detail about barriers to PA identified in Study IIIa, as well as pain and functional disability identified in Study IIIb is required to inform interventions which may help PwMSH to overcome such barriers. Therefore, qualitative studies with both PwMSH and their families, partners or spouses examining attitudes, barriers and facilitators to PA are warranted. Findings could then be used to inform personalised interventions which aim to improve PA and health outcomes in this population.
- Based off collective study findings, personalised interventions which are stratified according to individual level of morbidity are needed to address issues with PA and physical health in PwMSH. Longitudinal assessment of PA and physical health outcomes, in combination with clinical phenotypic presentation and potential comorbidities, would ensure appropriate intervention is delivered as required. This would strive to treat and prevent multiple aspects of chronic disease risk and address specific issues such as pain and functional disability in this population. Different types of exercise and lifestyle interventions may better suit different patients depending on their level of morbidity. Furthermore, multi-disciplinary input may be required for issues such as overweight or obesity, high blood pressure and chronic pain. Personalised PA and health interventions should consider specific barriers to PA, the involvement of family, spouses or partners, and the potential use of telehealth or e-health resources in order to optimise interventions and aim to maintain long-term health improvements.
- Lastly, the potential to expand a similar assessment of PA and health outcomes to the wider bleeding disorder community should also be considered in future studies. This may involve people with mild haemophilia, women with bleeding disorders, von Willebrand Disease and other rare factor deficiencies. The assessment of PA and chronic health risk also warrants exploration in the paediatric population with haemophilia. This would be particularly important in light of the low levels of PA and increasing rates of childhood obesity in the

general global paediatric population. The impact of primary prophylaxis and novel therapies would also be particularly interesting to examine in this context. Parental and care-provider attitudes towards PA would also be important to examine in paediatric studies.

7.5 Conclusion

To conclude, the findings of this thesis highlight that despite a uniform diagnosis, ageing adult PwMSH present with considerable inter-individual variation in physical health profile, potential for multi-morbidity and barriers to PA. This individual variation appears to be multi-factorial and may be further influenced by previous treatment regimens and iatrogenic infections, which predominantly affect the older adult population with moderate and severe haemophilia. Therefore, a 'one-size-fits-all' approach to health interventions will not suffice to improve the overall long-term health risk of this population. Health interventions should be personalised to individual PwMSH in order to effectively improve specific health outcomes and quality of life. Personalised, multi-disciplinary approaches to interventions to address physical inactivity, reduced physical fitness and cardiometabolic risk factors amongst the haemophilia population are warranted in future studies.

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Appendices

Appendix I: Search strategy for systematic review in Chapter 1

Medline (OVID)

1. exp Exercise/ OR exp Exercise Therapy/ OR exp Physical Fitness/ OR exp "physical education and training"/ OR exp "Exercise Movement Techniques"/ or physical endurance/ or exercise tolerance/ OR Physical Exertion/ or exp Sports/ or Dancing/
2. (strength$ or isometric$ or isotonic$ or isokinetic$).ti,ab.
3. (resistance adj3 train$).ti,ab.
4. ((physical$ or motion$) adj3 (fit$ or therap$)).ti,ab.
5. (treadmill$ or cross-train$ or rowing or sport$ OR exercis$ OR "physical activit$" OR aerobic$ OR run or jog$ or running OR walk or walks or walking OR gym$ OR yoga oR pilates OR "recreation$ activit$" OR zumba or salsa$ OR cycling or bicycle or bike or swim$ or dance or dancer$ or dances or dancing).ti,ab.
6. (circuit$ adj1 train$).ti,ab.
7. (keep$ adj1 (active or fit)).ti,ab.
8. or/1-7
9. exp Hemorrhage/ OR Hemarthrosis/
10. ((joint$ or spontaneous or Intraarticular or Intra-articular OR articular OR knee$ OR elbow$ OR ankle$) adj3 (bleed$ OR H?emorrhag$ OR h?emarthosis)).ti,ab.
11. H?emorrhag$.ti,ab.
12. or/9-11
13. Hemophilia A/ or Hemophilia B/
14. (H?emophili$).ti,ab.
15. or/13-14
16. 8 and 12 and15

EMBASE

1. 'exercise'/exp OR 'kinesiotherapy'/exp OR 'physical activity'/exp OR 'physical activity, capacity and performance'/de OR 'training'/de OR 'endurance'/de OR 'exercise tolerance'/de OR 'physical capacity'/de OR 'sport'/exp
1. (strength* or isometric* or isotonic* or isokinetic*):ti,ab
2. (resistance NEAR/3 train*):ti,ab
3. ((physical* or motion*) NEAR/3 (fit* or therap*)):ti,ab
4. (treadmill* or cross-train* or rowing or sport* OR exercise* OR "physical activit*" OR aerobic* OR run or jog* or running OR walk or walks or walking OR gym* OR yoga oR pilates OR "recreation* activit*" OR zumba or salsa* OR cycling or bicycle or bike or swim* or dance or dancer* or dances or dancing):ti,ab
5. (circuit* NEAR/1 train*):ti,ab
6. (keep* NEAR/1 (active or fit)):ti,ab
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
8. 'bleeding'/de OR 'hemarthrosis'/exp
9. ((joint* or spontaneous or Intraarticular or Intra-articular OR articular knee* OR elbow* OR ankle*) NEAR/3 (bleed* OR Hemorrhag* OR haemorrhag*)):ti,ab
10. (Hemorrhag* OR haemorrhag* OR hemarthosis OR haemarthosis):ti,ab
11. #9 OR #10 OR #11
12. 'hemophilia'/exp
13. (Hemophili* OR Haemophili*):ti,ab
14. #13 OR #14
15. #8 AND #12 AND #15

Cochrane

1. [mh "Exercise"] OR [mh "Exercise Therapy"] OR [mh "Physical Fitness”] OR [mh "physical education and training"] OR [mh "Exercise Movement Techniques"] OR [mh "physical endurance"] OR [mh ^”exercise tolerance”] OR [mh ^”Physical Exertion”] OR [mh ”Sports”] OR [mh ^”Dancing”]

2. (strength* or isometric* or isotonic* or isokinetic*):ti,ab,kw
3. (resistance NEAR/3 train*):ti,ab,kw
4. ((physical* or motion*) NEAR/3 (fit* or therap*)):ti,ab,kw
5. (treadmill* or cross-train* or rowing or sport* OR exercise* OR "physical activit*" OR aerobic* OR run or jog* or running OR walk or walks or walking OR gym* OR yoga oR pilates OR "recreation* activit*" OR zumba or salsa* OR cycling or bicycle or bike or swim* or dance or dancer* or dances or dancing):ti,ab,kw
6. (circuit* NEAR/1 train*):ti,ab,kw
7. (keep* NEAR/1 (active or fit)):ti,ab,kw
8. {OR #1-#7}
9. [mh "Hemorrhage"] OR [mh "hemarthrosis"]
10. (Hemorrhag* OR haemorrhag* OR hemarthosis OR haemarthosis):ti,ab,kw
11. ((joint* or spontaneous or Intraarticular or Intra-articular OR articular knee* OR elbow* OR ankle*) NEAR/3 (bleed* OR Hemorrhag* OR haemorrhag*)):ti,ab,kw
12. {OR #9-#11}
13. [mh "Hemophilia A"] OR [mh "Hemophilia B"]
14. (Hemophili* OR Haemophili*):ti,ab,kw
15. #13 OR #14
16. #8 AND #12 AND #15

CINAHL

1. (MH "Exercise+") OR (MH "Therapeutic Exercise+") OR (MH "Physical Fitness+") OR (MH "Physical Endurance+") OR (MH "Exertion") OR (MH "Exercise Intensity") OR (MH "Sports+") OR (MH "Dancing+")
1. TI (strength* or isometric* or isotonic* or isokinetic*) OR AB (strength* or isometric* or isotonic* or isokinetic*)
2. TI (resistance N3 train*) OR AB (resistance N3 train*)
3. TI ((physical* or motion*) N3 (fit* or therap*)) OR AB ((physical* or motion*) N3 (fit* or therap*))
4. TI(treadmill* or cross-train* or rowing or sport* OR exercise* OR "physical activit*" OR aerobic* OR run or jog* or running OR walk or walks or walking OR gym* OR yoga oR pilates OR "recreation* activit*" OR zumba or salsa* OR cycling or bicycle or bike or swim* or dance or dancer* or dances or dancing) OR AB (treadmill* or cross-train* or rowing or sport* OR exercise* OR "physical activit*" OR aerobic* OR run or jog* or running OR walk or walks or walking OR gym* OR yoga oR pilates OR "recreation* activit*" OR zumba or salsa* OR cycling or bicycle or bike or swim* or dance or dancer* or dances or dancing)
5. TI (circuit* N1 train*) OR AB (circuit* N1 train*)
6. TI (keep* N1 (active or fit)) OR AB (keep* N1 (active or fit))
7. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
8. (MH "Hemorrhage") OR (MH "Hemarthrosis")
9. TI((joint* or spontaneous or Intraarticular or Intra-articular OR articular knee* OR elbow* OR ankle*) N3 (bleed* OR H?emorrhag*)) OR AB ((joint* or spontaneous or Intraarticular or Intra-articular OR articular knee* OR elbow* OR ankle*) N3 (bleed* OR H?emorrhag*))
10. TI(Hemorrhag* OR haemorrhag* OR hemarthosis OR haemarthosis) OR AB(Hemorrhag* OR haemorrhag* OR hemarthosis OR haemarthosis)
11. S9 or S10 OR S11
12. (MH "Hemophilia")
13. TI (Hemophili* OR Haemophili*) OR AB (Hemophili* OR Haemophili*)
14. S13 OR S14
15. S8 AND S12 AND S15

Web of Science

1. TS=((strength* or isometric* or isotonic* or isokinetic*) OR (resistance NEAR/3 train*) OR ((physical* or motion*) NEAR/3 (fit* or therap*)) OR (treadmill* or cross-train* or rowing or sport* OR exercise* OR "physical activit*" OR aerobic* OR run or jog* or running OR walk or walks or walking OR gym* OR yoga oR pilates OR "recreation* activit*" OR zumba or salsa* OR cycling or bicycle or bike or swim* or dance or dancer* or dances or dancing) OR (circuit* NEAR/1 train*) OR (keep* NEAR/1 (active or fit)))
2. TS=(Hemorrhag* OR haemorrhag* OR hemarthosis OR haemarthosis)

3. TS=(((Joint OR spontaneous OR knee* OR elbow* OR ankle* OR Intraarticular) NEAR/3 (bleed* OR Hemorrhag* OR haemorrhag*)))
4. #2 OR #3
5. TS=((Hemophili* OR Haemophili*))
6. #1 AND #4 AND #5

7. #1 AND #4 AND #5

Appendix II: The STROBE checklist

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

		(*e*) Describe any sensitivity analyses

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix III: The AXIS critical appraisal tool

Reviewer: _____ **Study:** _____ **Date:** _____

Appraisal of Cross-sectional Studies

	Question	Yes	No	Don't know/ Comment
Introduction				
1	Were the aims/objectives of the study clear?			
Methods				
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?			
7	Were measures undertaken to address and categorise nonresponders?			
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?			
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?			
10	Is it clear what was used to determined statistical significance and/or precision estimates? (e.g. p-values, confidence intervals)			
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?			
Results				
12	Were the basic data adequately described?			
13	Does the response rate raise concerns about non-response bias?			
14	If appropriate, was information about non-responders described?			
15	Were the results internally consistent?			
16	Were the results presented for all the analyses described in the methods?			
Discussion				
17	Were the authors' discussions and conclusions justified by the results?			
18	Were the limitations of the study discussed?			
Other				
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?			

20	Was ethical approval or consent of participants attained?			

Appendix IV: Original ethical approval letter for Studies I-III

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hurlin Ph: 4142199
email: claire.hurlin@amnch.ie

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

Ms. Megan Kennedy
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
James's Street
Dublin 8

10th November 2017

Re : The Irish Personalized Approach to the Treatment of Haemophilia (iPATH) :An investigation of the relationship between physical health , physical activity and bleeding phgenotype in adults with haemophilia in Ireland

REC Reference: 2017- 11 - Chairman's Action (6)
(Please quote reference on all correspondence)

Dear Ms. Kennedy,

The REC is in receipt of your recent application to SJH/AMNCH Research Ethics Committee in which you queried ethical approval for the above named study.

The Chairman, Dr. Peter Lavin, on behalf of the Research Ethics Committee, has reviewed your correspondence and granted ethical approval for this study.

Yours sincerely,

Claire Hurlin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix V: Amendment approval letter (part 1)

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

SJH/AMNCH Research Ethics Committee Secretariat
researchethics@tuh.ie

Ms Megan Kennedy,
iPATH Physiotherapist,
Discipline of Physiotherapy,
Trinity Centre for Health Sciences,
St. James's Hospital, Dublin 8.

10th May 2019

Re: The Irish personalised approach to the treatment of Haemophilia (iPATH): An investigation of the relationship between physical health, physical activity and bleeding phenotype in adults with Haemophilia in Ireland

REC Reference: 2019-05 List 17 (15)
Previous REC Reference:
(Please quote reference on all correspondence)

EudraCT Number: N/A

Date of Valid Submission to REC: 24.04.2019
Date of Ethical Review: 08.05.2019
R&I application Number: N/A

Dear Ms Kennedy,

Thank you for your correspondence in which you submitted an amendment for the above named study.

The Chairman has reviewed the documentation you submitted and has given full ethical approval for this amendment subject to the following:

- Please add the data processors to the PIL

The following documents were reviewed:

- Non-clinical amendment form, dated 25.04.2019
- Cover Letter, dated 25.04.2019
- PIL, CF, V3, dated 25.04.2019
- Modifiable Activity Questionnaire, V1, dated 25.04.2019

Applicants must submit an annual report for ongoing projects and an end of project report upon completion of the study. It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018. Additionally, please note for documents submitted for GDPR purposes that the REC and the Chair are not confirming that you're documents are GDPR compliant, they are approving the document from an ethical perspective.

Yours sincerely,

Appendix V: Amendment approval letter (part 2)

Tallaght University Hospital | Ospidéal Ollscoile Thamhlachta

An Academic Partner of Trinity College Dublin

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

Ms Megan Kennedy,
St James's Hospital,
James' Street,
Dublin 8

31st July 2019

REF: The Irish Personalised Approach to the Treatment of Haemophilia (iPATH): An Investigation of the Relationship between Physical activity and Bleeding Phenotype in Adults with Haemophilia in Ireland

REC: 2019-07 List 27 (28)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 13.05.2019
Date of Ethical Review: 31.07.2019
R&I Application Number: N/A

Dear Ms Kennedy,

Thank you for your correspondence in which you sent in a response to the Committee's letter which detailed the Committee's queries and concerns in relation to the amendment submitted for the above referenced research study.

The Chairman, Prof. Richard Dean, on behalf of the Research Ethics Committee, has reviewed your correspondence and has given full approval.

The following documents were reviewed:

- PIL, V4, dated 4th May 2019

*Applicants must submit an annual report for ongoing projects and an end of project report upon completion of the study. It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018. **Additionally, please note for documents submitted for GDPR purposes that the REC and the Chair are not confirming that you're documents are GDPR compliant, they are approving the document from an ethical perspective.***

Yours sincerely,

Sadhbh O'Neill

REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix VI: Ethical approval letter for Study IV (part 1)

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

JREC Reference: 2020-11 List 43 – Amendment (7)

Ms Megan Kennedy,
St James's Hospital,
James' Street,
Dublin 8

30th November 2020

REF: Irish Personalised Approach to the Treatment of Haemophilia Project

REC: 2020-11 List 43 – Amendment (7)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 22.09.2020
Date of Ethical Review: 06.11.2020

Dear Ms Kennedy,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the amendment you submitted to the SJH/TUH JREC for the above named study and has given **PROVISIONAL APPROVAL** for this amendment. The following comments were made:

- The QOL questionnaire is anonymous. How will the patient be followed if they highlight distress in Q18 of the questionnaire?

The following documents were reviewed:

- iPATH Physical Activity and Quality of Life Questionnaire Version 2 22nd September 2020.docx
- iPATH Physical Activity cleaning and disinfection protocol Version 2 22-09-20.docx
- iPATH Physical Activity Study- Amendment Application Letter REC 22nd Sept 2020.pdf
- [illegible]
- TUH_SJH_REC_Non_Clinical_Amendment_Request_Form iPATH Physical Activity Study.pdf

Please note that ethical approval for this study is only active under the following conditions:

1. ***Applicants must submit an annual report for ongoing projects.***
2. ***Applicants must submit an end of study declaration/end of study report upon completion of the study.***
3. ***All adverse events must be reported to the JREC.***
4. ***All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.***

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Seamus O'Reilly

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix VI: Ethical approval letter for Study IV (part 2)

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

JREC Reference: 2021-01 List 03 – Response to Comments (2)

Ms Megan Kennedy,
St James's Hospital,
James' Street,
Dublin 8

20th January 2021

REF: The Irish Personalised Approach to the Treatment of Haemophilia (iPATH): An Investigation of the Relationship between Physical Activity, Health and Bleeding Phenotype in Adults with Haemophilia in Ireland

REC: 2021-01 List 3 – Response to Comments (2)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 02.12.2020
Date of Ethical Review: 15.01.2021

Dear Ms Kennedy,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the Response to the Committees comments you submitted and has given **FULL** approval for the study to proceed.

The following documents were reviewed:

- iPATH Physical Activity and Quality of Life Questionnaire Version 3 2nd December 2020.docx
- iPATH Physical Activity Study_Amendment Request Letter REC 2nd December 2020.pdf
- TUH SJH Rec_Non_Clinical_Amendment_Request_Form iPATH Physical Activity Study_2nd December 2020.pdf

Please note that ethical approval for this study is only active under the following conditions:

- ✓ ***Applicants must submit an annual report for ongoing projects.***
- ✓ ***Applicants must submit an end of study declaration/end of study report upon completion of the study.***
- ✓ ***All adverse events must be reported to the JREC.***
- ✓ ***All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.***

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Sadhbh O'Neill

REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix VII: Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Appendix VIII: Participant information leaflet (Haemophilia group) for Studies I-III

Patient Information Leaflet

The Irish Personalized Approach to the Treatment of Haemophilia (iPATH): An investigation of the relationship between physical health, physical activity and bleeding phenotype in adults with haemophilia in Ireland.

The Research Team:

Lead Investigator: Prof. John Gormley

Co-Investigators: Prof. James O' Donnell & Dr. Michelle Lavin

Research Physiotherapist: Ms. Megan Kennedy

INTRODUCTION: Before you decide whether or not you wish to take part in this study, you should read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'. You may wish to discuss it with your family, friends or medical team.

WHO IS CARRYING OUT THIS RESEARCH? Researchers from the School of Physiotherapy in Trinity College, Dublin are carrying out this study to investigate how healthy and active people with haemophilia in Ireland are. They are also investigating how health relates to bleeding tendencies between individuals.

PART 1 – THE STUDY

WHY THIS STUDY IS BEING DONE AND WHY HAVE YOU BEEN ASKED TO TAKE PART?
Research to date in other haemophilia populations has suggested that they tend to have lower levels of physical activity and fitness in comparison with the general population. The association between low physical activity, fitness and strength may play a role in your risk of bleeding. Changing activity and exercise habits may play a vital role in the management of treatment regimens, bleeds and joint damage in the long-run. The researchers of this study want to find out more about how fit and healthy the population of adults with haemophilia in Ireland are and how it affects bleeding as well as their overall health and well-being. You are being asked to participate because you have severe of moderate haemophilia.

AIM: The aim of this study is to establish the association between health, fitness, physical activity with bleeding tendency in people with haemophilia in Ireland.

WHAT IS INVOLVED IF YOU AGREE TO PARTICIPATE: If you are suitable and decide to take part in this study you will be asked to attend an appointment at the Clinical Research Facility in St James's Hospital, Dublin for a physiotherapy assessment. Most of the tests require you to physically exert yourself at a gentle level. Before your visit, you will be asked to ensure you have taken prophylaxis on the day of the assessment. A detailed blood pressure analysis will also be performed prior to commencing the exercise tests. The visit should take approximately 60-90 minutes of your time in total. Even if the study has started, you can still opt out. You don't have to give a reason. If you wish to opt out, please contact Ms. Megan Kennedy (see contact details at the bottom of this leaflet) who will be able to organise this for you.

Information about your gender, age, clinical information about haemophilia, such as bleeds, treatment history, joint health scores, bone mineral density and any other relevant past medical history will be gathered as these are factors which may affect how active you are.

You will be asked to participate in a series of health and fitness assessments as follows:

1. **BODY COMPOSITION ANALYSIS:** We will ask you to stand on a machine and your height as well as the amount of fat, water and muscle in your body will be checked automatically. Waist circumference and body weight will also be measured manually.

2. **PHYSICAL FITNESS TESTS:** You will be asked to do a **6-minute walk test** which requires you to walk continuously at your own comfortable pace for 6 minutes in total. Your heart and breathing rate will be monitored throughout the test. You can stop the test at any point if you need to.

Fitness Test: Your fitness will be tested using an exercise test conducted on a stationary bike or a treadmill. These tests measure how well your muscles use oxygen when you exercise. This essentially tells us how fit you are. If you have pain or limitations in your knees or ankles, this test may not be suitable for you and you do not need to complete this section.

Strength Test: You will be asked to do a grip strength test by gripping a machine to estimate your overall upper body strength. You will also be asked to do a leg strength test using a similar device which measures the force of muscle contraction in your legs.

Balance Test: You will be asked to do a One-Leg-Stand test for a maximum of 30 seconds to check your balance. A researcher will be standing near you to ensure your safety.

3. **Physical Activity Monitoring:** The next component of the testing procedure involves measuring your levels of physical activity on a day-to-day basis. You will be given a small device called an accelerometer that sits on a belt that you will wear for 1 week during the day. This device is about the size of a matchbox and records your movements while awake. This device measures activity during the day such as walking, running, cycling, doing housework, etc. We will provide you with an information leaflet and an activity log sheet to record any activity you partook in when not wearing the accelerometer (e.g. swimming). We will provide you with a stamped and addressed envelope in which to place the device in to send back to us after 1 week or you can drop it into the clinic if more convenient. **The device is not to be worn in the shower/bath or while swimming as it is not water – resistant**. Please see the images for an example of what an accelerometer looks like. You will also be asked to fill out a questionnaire regarding your participation in sport and exercise currently as well as during childhood.

4. **QUESTIONNAIRES:** Lastly, you will be asked to fill out three questionnaires. One questionnaire seeks to gather information about your experiences living as an adult with haemophilia. Another questionnaire will ask questions specifically relating to barriers to physical activity. The final questionnaire will ask you more detail about physical activity and sport played in the last year as well as some additional questions regarding your treatment and bleed history in relation to physical activity.

5. **MEDICAL RECORD ACCESS**: The research team asks for your consent to access your medical records and clinical information from the database at the NCC for analysis

purposes for this study. Any clinically relevant information from the assessment will be stored as a part of your medical record as well.

BENEFITS: Full analysis of your health, fitness levels and body composition measurements will be provided upon completion of the assessments if you desire in the form of an individualised health report, which may be of potential benefit in informing your future healthcare and lifestyle choices. Participating in this study will also benefit this field of research by adding to it.

RISKS: During exercise testing participants may experience bodily pain, chest pain, fatigue, dizziness or difficulty breathing during and may wish to stop the test. If so the test will be stopped immediately. The exercise test will also be stopped if you wish to or if there is any medical concern and you will be reviewed by a doctor from the haemophilia team. If you have had joint pain or a bleed in the previous 2 weeks before your assessment, it may be cancelled or rescheduled until the issue has fully resolved.

All your personal data will be assigned a study code. Your personal identifiers (name, address, hospital number) will be removed from all clinical data collected in this study and only the code used. All data will be stored securely using password protection and restricted access. In the unlikely event of a data breach, your rights are unaffected, however, your name and identifying information will not be kept with the research data.

INCLUSION CRITERIA: Participants must meet the following inclusion criteria:

1. Aged 18 and above.
2. Moderate or severe haemophilia A or B.
3. Deemed medically suitable by the research team.

EXCLUSION FROM PARTICIPATION

1. Participants who are deemed medically unstable to exercise
2. Uncontrolled blood pressure abnormalities (e.g. hypertension/hypotension)
3. Fitted electronic device (e.g. pacemaker)
4. Unable to provide informed consent
5. Acute joint or muscular bleed within previous 2 weeks
6. Exclusion for any other reason deemed appropriate by the research team

ON THE DAY OF THE ASSESSMENT:

- Please wear loose clothes and comfortable shoes that you will be able to exercise in.
- It would be best to bring a towel, shower gel, and change of clothes as you may wish to shower after testing.
- Please try to drive or use public transport to get to the testing venue and avoid walking or cycling on the day of your visit if possible as it will make for more accurate results of your fitness test if you have not done much physical activity prior to testing. Please remember not to eat any heavy meals directly before testing if possible. Please also limit your liquid intake for 12-hours before. Water is allowed during this time but please refrain from caffeine, herbal teas or other drink products.
- Please also refrain from tobacco, alcohol and strenuous physical activity for 24 hours prior to their assessment. This will help improve accuracy of your test results.

PART 2 – DATA PROTECTION

WHAT INFORMATION ABOUT YOU (PERSONAL DATA) WILL BE USED AS PART OF THIS STUDY AND WHY IS IT BEING USED?

Personal data collected about you will include your gender, age, clinical information about haemophilia, bleeds, treatment history, joint health scores, bone mineral density and any other relevant past medical history will be gathered from the clinical database and medical records as these are factors which may affect how active you are. Information on your body

composition, strength and fitness, blood pressure, physical activity levels for 1 week recorded by the ActiGraph accelerometer, physical activity questionnaires and patient reported outcomes, burdens and experiences questionnaire will be collected. This information is needed to determine the aims of the study which are to examine the relationship between physical activity, health and fitness and bleeding tendencies in adults with haemophilia. Your physical activity levels will also be profiled (placed into a category) as to whether they are currently meeting recommended physical activity guidelines.

HOW WILL YOUR PERSONAL DATA BE PROTECTED?

All of your information is assigned a study ID code by the research team (in a process called pseudonymisation). This coding process is linked to your personal data and is intended to mask your identity. **Personal identifiers, such as your name or date of birth, are never used to label your study information.** The codes linked to your personal information are secured in a locked cabinet and on a password protected database in the National Coagulation Centre. Your study results will be coded and stored on an electronic database in a secure password protected PC in a locked office and any paper forms will be stored in a locked cabinet in the Trinity Centre for Health Sciences. Only personal data which is relevant for the purpose of the study is used (a concept called data minimisation).

WHO HAS ACCESS TO YOUR DATA AND HOW WILL YOUR DATA BE USED?

Only the research team have access to your data and will be involved in analysing and processing it. The data processors include the study investigators and research physiotherapist. Your results will be grouped with other study results and analysed to establish your physical activity levels as well as its association with the other factors outlined in the aims section of this leaflet. The overall study findings will be published in international peer reviewed journals and be shared within presentations at national and international meetings. Your personal data will remain pseudonymised and your name and personal details will not be published or disclosed to anyone outside of this study.

WHO CONTROLS ACCESS TO YOUR DATA, HOW YOUR DATA WILL BE STORED AND HOW LONG WILL YOUR DATA BE STORED FOR:

The study investigators outlined control access to your personal data. All information relating to you will be stored and locked in a secure office in the NCC, only accessible by the research team. Your study results will be coded (pseudonymised) and stored on an electronic database in a secure password protected PC in a locked office in the Trinity Centre for Health Sciences. Any paper forms (such as the consent form) will be stored in your medical file and a copy will be stored in the research file (which will be securely stored and locked away in a locked cabinet in the NCC). Data will be stored for a total of 10 years to allow sufficient time for analysis and potential publications related to the research. It will then be destroyed appropriately by the research team.

IS THERE ANY RISK INVOLVED WITH PROCESSING AND STORING YOUR DATA AND WHAT WILL BE DONE IF THERE IS A BREACH: Considering sensitive personal data relating to your health and behaviour is involved, in the unlikely event of a data breach (i.e. data being mislaid, lost or stolen) you will be notified as soon as possible and it will be reported immediately to the Data Protection
Commissioner. Please be assured your data will be secure using pseudonymisation (coded), minimisation (only relevant data is collected) and stored securely (in password protected electronic databases and locked cabinets between the NCC and a locked office in the Trinity Centre for Health Sciences accessible only to the research team).

WHAT IS THE LAWFUL BASIS TO USE YOUR PERSONAL DATA?

Your data will be processed under the lawful basis of Article 6(1)(e) and 9(2)(j) of the EU General Data Protection Regulation Act 2016.

IF YOU WITHDRAW FROM THE STUDY WHAT WILL HAPPEN TO YOUR DATA:

You may withdraw consent from the study if you so wish at any time and your data will not be included in the analysis, it will be securely destroyed by the study investigators.

For any data queries/ complaints in relation to your rights under General Data Protection Regulations, please see contact information for the Data Protection Officer, Trinity College Dublin:

Data Protection Officer, Trinity College Dublin.

Email: dataprotection@tcd.ie

With regards to your personal data rights under GDPR, you have the right to the following (unless your request would make it impossible or make it very difficult to carry out the research):

You have the right to…

- Access your data
- Rectify or correct any mistakes with your data
- Have your data erased or deleted
- Restrict or limit processing of your data or how it's used
- Data portability (moving your data from one controller to another)
- Object to or stopping the processing or profiling of your data
- Lodge a complaint to the Data Protection Commissioner (Contact: +353 57 8684800 or +353 (0)761 104 800; https://dataprotection.ie/en/contact).

PART 3 – COSTS, FUNDING & APPROVAL

VOLUNTARY PARTICIPATION: If you have volunteered to participate in this study, you may withdraw participation at any time. If you decide not to participate, or if you withdraw consent, you will not be penalized and will not give up any benefits which you had before entering the study. You should not feel in any way obliged to take part in this study. If you wish to seek more information about this study, please contact the research physiotherapist (Ms. Megan Kennedy) directly.

WITHDRAWAL FROM THE STUDY: You may withdraw consent from the study if you so wish at any time and your data will not be included in the analysis.

COMPENSATION: The research team covered by standard clinical indemnity. Nothing in this document restricts or curtails your rights.

STOPPING THE STUDY: You understand that the research team may stop your participation in the study at any time without your consent.

WILL IT COST YOU TO TAKE PART? There are no financial costs involved with partaking in this study.

HAS THIS STUDY BEEN APPROVED BY A RESEARCH ETHICS COMMITTEE? WHO IS FUNDING THE STUDY? WILL RESULTS BE USED FOR COMMERCIAL PURPOSES? This research project has ethical approval Tallaght/ St. James's Research Ethics Committee approval received on 10th November 2017. This study is funded in part by a SFI Strategic Partnership Programme research grant from Science Foundation (SFI) and research support from Shire US Inc. Study results will not be used for commercial purposes.

PART 4 – FURTHER INFORMATION

For more information or answers to your questions about the study, your participation in the study and your rights or if you wish to make a complaint, please see the contact details below:

Research Physiotherapist and Data Processor: Ms. Megan Kennedy, BSc (Hons) Physiotherapy.

Discipline of Physiotherapy, Trinity Centre for Health Sciences, St James's Hospital.

Contact Details: Tel (01)8963613; Email: kennedme@tcd.ie

Lead investigator and Data Controller: Prof. John Gormley, Trinity College Dublin

Contact Details: Tel (01) 8962121; Email: jgormley@tcd.ie

Data Protection Officer's Identity: Data Protection Trinity College Dublin

Contact Details: dataprotection@tcd.ie

Will I be contacted again?

You may be contacted again by the researchers in relation to your study results if you express that would like to receive feedback on them. With your explicit consent, you may also be contacted again by the researchers in relation to the current as well as other research studies of this nature.

Appendix VIII: Participant information leaflet (Control group) for Studies I-III

Participant Information Leaflet

An Investigation of Physical Activity, Cardiometabolic Health and Fitness in Healthy Men.

The Research Team:

Lead Investigator: Prof. John Gormley **Co-Investigator/ Research Physiotherapist:** Ms. Megan Kennedy

INTRODUCTION: Before you decide whether or not you wish to take part in this study, you should read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'. You may wish to discuss it with your family, friends or medical team.

WHO IS CARRYING OUT THIS RESEARCH? Researchers from the Discipline of Physiotherapy in Trinity College, Dublin are carrying out this study.

PART 1 – THE STUDY

WHY THIS STUDY IS BEING DONE AND WHY HAVE YOU BEEN ASKED TO TAKE PART?
Good quality research in patient studies needs similar information from healthy individuals to be able to tell if patients are more affected by disease than healthy individuals in certain areas. The researchers of this study want to collect information about physical activity, fitness and cardiometabolic risk in healthy men. Results from this study will be further analysed and compared with the same information in another hospital study which involves patients. This information will be used to determine if patients are more or less physically active, fit or at risk of cardiometabolic disease than healthy individuals. You have been asked to take part because healthy men 18 years old or older are needed for this study.

AIM: The main aim of this study is to investigate physical activity, fitness and cardiometabolic risk in healthy men. The other aim is to compare this information with that of a patient group from another study.

WHAT IS INVOLVED IF YOU AGREE TO PARTICIPATE: If you are suitable and decide to take part in this study you will be asked to attend an appointment at the Clinical Research Facility in St James's Hospital, Dublin for a physiotherapy assessment. Most of the tests require you to physically exert yourself at a gentle level. A detailed blood pressure analysis will also be performed prior to commencing the exercise tests. The visit should take approximately 60-90 minutes of your time in total. Even if the study has started, you can still opt out. You don't have to give a reason. If you wish to opt out, please contact Ms. Megan Kennedy (see contact details at the bottom of this leaflet) who will be able to organise this for you.

Information about your gender, age, ethnicity, occupation/ area of study, smoking status, relevant past medical or family history will be gathered as these are factors which may affect how active and fit you are. You will be asked to participate in a series of health and fitness assessments as follows:

1. **BODY COMPOSITION ANALYSIS:** We will ask you to stand on a machine that will measure your height as well as the amount of fat, water and muscle in your body automatically. Waist circumference and body weight will also be measured manually.

2. **PHYSICAL FITNESS TESTS:**

6-Minute Walk Test: You will be asked to do a **6-minute walk test** which requires you to walk continuously at your own comfortable pace for 6 minutes in total. Your heart and breathing rate will be monitored throughout the test. You can stop the test at any point if you need to.

Fitness Test: Your fitness will be tested using an exercise test conducted on a stationary bike or a treadmill. These tests measure how well your muscles use oxygen when you exercise. This essentially tells us how fit you are.

Strength Test: You will be asked to do a grip strength test by gripping a machine to estimate your overall upper body strength. You will also be asked to do a leg strength which involves squats.

Balance Test: You will be asked to do a One-Leg-Stand test to check your balance. A researcher will be standing near you to ensure your safety.

3. **PHYSICAL ACTIVITY MONITORING:** The next component of the testing procedure involves measuring your levels of physical activity on a day-to-day basis. You will be given a small device called an accelerometer that sits on a belt that you will wear for 1 week during the day. This device is about the size of a matchbox and records your movements while awake. This device measures activity during the day such as walking running, cycling, doing housework, etc. We will provide you with an information leaflet and an activity log sheet to record any activity you partook in when not wearing the accelerometer (e.g. swimming). We will provide you with a stamped and addressed envelope in which to place the device in to send back to us after 1 week or you can drop it into the research office if more convenient. **The device is not to be worn in the shower/bath or while swimming as it is not water – resistant**. Please see the images for an example of what an accelerometer looks like. You will also be asked to fill out a questionnaire regarding your participation in sport and exercise currently as well as during childhood.

4. **QUESTIONNAIRES:** Lastly, you will be asked to fill out a questionnaire relating to barriers to physical activity. Another questionnaire will ask you more detail about physical activity and sport played in the last year as well as some additional questions regarding your childhood physical activity levels.

BENEFITS: Full analysis of your health, fitness levels and body composition measurements will be provided upon completion of the assessments if you desire in the form of an individualised health report, which may be of potential benefit in informing your future

healthcare and lifestyle choices. Participating in this study will also benefit this field of research by adding to it.

RISKS: During exercise testing participants may experience bodily pain, chest pain, fatigue, dizziness or difficulty breathing during and may wish to stop the test. If so the test will be stopped immediately. The exercise test will also be stopped if you wish to or if there is any medical concern and you will be referred to a medical team or your GP.

INCLUSION CRITERIA: Participants must meet the following inclusion criteria:

- Healthy male adults aged 18 or over.
- Fluent in English.
- Free of mental disability or illness that would affect the ability to give informed, explicit consent.

EXCLUSION FROM PARTICIPATION

- Unstable or un-managed cardiac/respiratory/metabolic conditions.
- Neurological or musculoskeletal disorders.
- Recent injury or pain.
- Cancer.
- Mental illness.
- Chronic infectious disease (Hepatitis C/ HIV/ AIDS).
- Recent infection or illness.
- Those who have high cardiovascular risk without previous investigation.
- Exclusion for any other reason deemed appropriate by the research team.

ON THE DAY OF THE ASSESSMENT:

- Please wear loose clothes and comfortable shoes that you will be able to exercise in.
- A towel, shower gel, and change of clothes if you wish to shower after testing.
- Please try to drive or use public transport to get to the testing venue and avoid walking or cycling on the day of your visit if possible as it will make for more accurate results of your fitness test if you have not done much physical activity prior to testing. Please remember not to eat any heavy meals directly before testing if possible. Please also limit your liquid intake for 4-hours before. Water is allowed during this time but please refrain from caffeine, herbal teas or other drink products.
- Please also refrain from tobacco, alcohol and strenuous physical activity for 24 hours prior to the assessment. This will help improve accuracy of your test results.

PART 2 – DATA PROTECTION

WHAT INFORMATION ABOUT YOU (PERSONAL DATA) WILL BE USED AS PART OF THIS STUDY AND WHY IS IT BEING USED? Personal data collected about you will include your gender, age, ethnicity, occupation/ area of study, smoking status, relevant past medical or family history as these are factors which may affect how active and fit you are. Information on your body composition, strength and fitness, blood pressure, physical activity levels for 1 week recorded by the ActiGraph accelerometer and physical activity questionnaires will be collected. This information is needed to determine the aims of the study as mentioned the last section. Your physical activity levels will also be profiled (placed into a category) as to whether they are currently meeting recommended physical activity guidelines.

HOW WILL YOUR PERSONAL DATA BE PROTECTED? All of your information is assigned a study ID code by the research team (in a process called pseudonymisation). This coding process is linked to your personal data and is intended to mask your identity. **Personal identifiers, such as your name or date of birth, are never used to label your study information.** The codes linked to your personal information and your study results are secured

in a cabinet and on a password protected database in a locked office in the Trinity Centre for Health Sciences. Only personal data which is relevant for the purpose of the study is used (a concept called data minimisation). Once your results have been analysed and fed back to you, the code will be removed from your data and destroyed (i.e. erased) in a process called anonymization. Your data cannot be traced back to you when it is fully anonymised. Your anonymised data will then be stored and used for further analysis and comparative purposes with a patient study group.

WHO HAS ACCESS TO YOUR DATA AND HOW WILL YOUR DATA BE USED? Only the research team have access to your data and will be involved in analysing and processing it. The data processors include the study investigators and research physiotherapist. Your results will be grouped with other study results and analysed to establish your physical activity levels, fitness and cardiometabolic health. These study findings can be fed back to you if you wish. The overall study findings will be then anonymized and compared with similar information from a patient study group. Overall findings of these studies will be published in international peer reviewed journals and be shared within presentations at national and international meetings. Your personal data will remain anonymised and your name and personal details will not be published or disclosed to anyone outside of this study.

WHO CONTROLS ACCESS TO YOUR DATA, HOW YOUR DATA WILL BE STORED AND HOW LONG
WILL YOUR DATA BE STORED FOR: The lead investigator in conjunction with Trinity College Dublin and St. James's Hospital control access to your personal data. All information relating to you will be stored and locked in a secure office in the Trinity Centre for Health Sciences, only accessible by the research team. Your information and study results are secured in a locked cabinet and on a password protected database in a locked office in the Trinity Centre for Health Sciences. Your study results will be coded (pseudonymised) initially and this code will later be erased (anonymized) for further data analysis and storage. Anonymised data will be stored for a total of 10 years to allow sufficient time for analysis and potential publications related to the research. It will then be destroyed appropriately by the research team.

IS THERE ANY RISK INVOLVED WITH PROCESSING AND STORING YOUR DATA AND WHAT WILL BE DONE IF THERE IS A BREACH: Considering sensitive personal data relating to your health and behaviour is involved, in the unlikely event of a data breach (i.e. data being mislaid, lost or stolen) you will be notified as soon as possible and it will be reported immediately to the Data Protection Commissioner. Please be assured your data will be secure using pseudonymisation (coded), minimisation (only relevant data is collected) and subsequently anonymisation (not traceable to you) and will be stored securely (in password protected electronic databases and locked cabinets in a locked office in the Trinity Centre for Health Sciences accessible only to the research team).

WHAT IS THE LAWFUL BASIS TO USE YOUR PERSONAL DATA? Your data will be processed under the lawful basis of Article 6(1)(e) and 9(2)(j) of the EU General Data Protection Regulation Act 2016.

IF YOU WITHDRAW FROM THE STUDY WHAT WILL HAPPEN TO YOUR DATA:

You may withdraw consent from the study if you so wish at any time and your data will not be included in the analysis, it will be securely destroyed by the study investigators.

For any data queries/ complaints in relation to your rights under General Data Protection Regulations, please see contact information for the Data Protection Officer, Trinity College Dublin:

Data Protection Trinity College Dublin and Data Protection St. James's Hospital.

Email: dataprotection@tcd.ie or dataprotection@stjames.ie

With regards to your personal data rights under GDPR, you have the right to the following (unless your request would make it impossible or make it very difficult to carry out the research):

You have the right to…

- Access your data
- Rectify or correct any mistakes with your data
- Have your data erased or deleted
- Restrict or limit processing of your data or how it's used
- Data portability (moving your data from one controller to another)
- Object to or stopping the processing or profiling of your data
- Lodge a complaint to the Data Protection Commissioner (Contact: +353 57 8684800 or +353 (0)761 104 800; https://dataprotection.ie/en/contact).

PART 3 – COSTS, FUNDING & APPROVAL

VOLUNTARY PARTICIPATION: If you have volunteered to participate in this study, you may withdraw participation at any time. If you decide not to participate, or if you withdraw consent, you will not be penalized and will not give up any benefits which you had before entering the study. You should not feel in any way obliged to take part in this study. If you wish to seek more information about this study, please contact the research physiotherapist (Ms. Megan Kennedy) directly.

WITHDRAWAL FROM THE STUDY: You may withdraw consent from the study if you so wish at any time and your data will not be included in the analysis.

COMPENSATION: The research team covered by standard clinical indemnity. Nothing in this document restricts or curtails your rights.

STOPPING THE STUDY: You understand that the research team may stop your participation in the study at any time without your consent.

WILL IT COST YOU TO TAKE PART? There are no financial costs involved with partaking in this study.

HAS THIS STUDY BEEN APPROVED BY A RESEARCH ETHICS COMMITTEE? WHO IS FUNDING THE STUDY? WILL RESULTS BE USED FOR COMMERCIAL PURPOSES? This research project has ethical approval from St James's Hospital/Tallaght University Hospital Joint Research Committee received on 10th July 2019. This study is funded in part by a SFI Strategic Partnership Programme research grant from Science Foundation (SFI). Study results will not be used for commercial purposes.

PART 4 – FURTHER INFORMATION

For more information or answers to your questions about the study, your participation in the study and your rights or if you wish to make a complaint, please see the contact details below:

Research Physiotherapist: Ms. Megan Kennedy, BSc (Hons) Physiotherapy.
Discipline of Physiotherapy, Trinity Centre for Health Sciences, St James's Hospital.

Contact Details: Tel (01) 8963613; Email: kennedme@tcd.ie

Lead investigator: Prof. John Gormley, Trinity College Dublin

Contact Details: Tel (01) 8962121; Email: jgormley@tcd.ie

Data Processors and Controllers: Trinity College Dublin and St. James's Hospital

Data Protection Officer's Identity: Data Protection Trinity College Dublin and Data Protection St. James's Hospital

Contact Details: dataprotection@tcd.ie or dataprotection@stjames.ie

Will I be contacted again?

You may be contacted again by the researchers in relation to your study results if you express that would like to receive feedback on them. With your explicit consent, you may also be contacted again by the researchers in relation to the current as well as other research studies of this nature.

Appendix IX: Informed consent form (Haemophilia group)

INFORMED CONSENT FORM

The Irish Personalized Approach to the Treatment of Haemophilia (iPATH): An investigation of the relationship between physical health, physical activity and bleeding phenotype in adults with haemophilia in Ireland.

Research Team:

Lead Investigator: Dr. John Gormley

Co-Investigators: Prof. James O'Donnell & Dr. Michelle Lavin

Research Physiotherapist: Ms. Megan Kennedy

Research Nurse: Ms. Anjali Patel

PART 1 – EXPLICIT, INFORMED, VOLUNTARY CONSENT TO PARTAKE IN THIS STUDY.		
I understand I will be asked to undertake a research assessment which will collect data about my activity, haemophilia and factors related to haemophilia that may influence my activity as outlined in the information leaflet. I agree for the research team to access my medical records. I have been assured that information about me will be kept private and confidential.	YES □	NO □
I understand I am asked to wear the ActiGraph accelerometer for 1 week and record in the provided activity diary as explained. I will then send the ActiGraph back to the investigator by whatever means are most convenient for me.	YES □	NO □
I am aware of the risks involved in this study that were outlined in the patient information leaflet. I have been made aware of what will happen in the case of a data breach. I am aware of the benefits and alternatives of this research study.	YES □	NO □
I confirm that I have read and fully understood the relevant Participant Information Leaflet (version 4, 13th May 2019) provided to me.	YES □	NO □
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES □	NO □
I have received enough information about this study and understand what is involved if I agree to participate.	YES □	NO □
I understand that I am free to withdraw from the study at any time without giving a reason with no consequence.	YES □	NO □
I agree to be contacted by researchers as part of this study.	YES □	NO □

I freely and voluntarily consent to take part in this research study having been fully informed of the risks, benefits and alternatives.	YES □	NO □

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

***You are now entering a separate part of this consent form relating to data protection*.**

PART 2 – EXPLICIT, INFORMED CONSENT REGARDING DATA PROTECTION.

I understand that all of my data will be pseudonymised and minimised for this study "The Irish Personalized Approach to the Treatment of Haemophilia (iPATH): An investigation of the relationship between physical health, physical activity and bleeding phenotype in adults with haemophilia in Ireland." The words pseudonymisation and minimisation have been explained to me.	YES □	NO □
I understand my name or other personal identifiers will not be disclosed to anybody not involved with this study and my personal data will be kept strictly confidential.	YES □	NO □
I understand the research team will be processing my data and the Lead Investigator in conjunction with Trinity College Dublin is in control of my data.	YES □	NO □

I understand that my data will be used for study analysis, published in peer reviewed journals, in presentations and may be disseminated at conferences but my data will remain confidential and none of my personal identifiers will be disclosed in these circumstances.	YES □	NO □
I understand how my data will be stored (pseudonymised and minimised in secure locations only accessible to the research team) and that it will be stored for a total of 10 years and will then be securely destroyed by the study investigators.	YES □	NO □
I have been made aware of my rights under the General Data Protection Regulations and contact details of the Data Protection Officer and Data Commissioner have been provided to me in the Patient Information Leaflet.	YES □	NO □
I have read and understood the personal data protection section of the Participant Information Leaflet (version 4, 13th May 2019).	YES □	NO □
I have had the opportunity to discuss data protection in this study and I have received satisfactory answers to all my questions.	YES □	NO □
I understand that I am free to withdraw from the study at any time without giving a reason with no consequence and my personal data will not be used and will be securely destroyed.	YES □	NO □
I freely and voluntarily consent to allow the researcher's use of my information (personal data) as part of this study as outlined in the information leaflet.	YES □	NO □

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature of data protection in this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher’s Name (Block Capitals):	
Researcher’s Title & Qualifications:	
Researcher’s Signature:	
Date:	

Appendix IX: Informed consent form (Control group)

INFORMED CONSENT FORM

An Investigation of Physical Activity, Cardiometabolic Health and Fitness in Healthy Men

Research Team:

Lead Investigator: Prof. John Gormley

Co-Investigator/ Research Physiotherapist: Ms. Megan Kennedy

PART 1 – EXPLICIT, INFORMED, VOLUNTARY CONSENT TO PARTAKE IN THIS STUDY.		
I understand I will be asked to undertake a research assessment which will collect data about my physical activity, fitness and cardiometabolic health as outlined in the information leaflet and that my data will be used as normative data for comparative purposes with a clinical population group. I have been assured that information about me will be kept private and confidential.	YES ☐	NO ☐
I understand I am asked to wear the ActiGraph accelerometer for 1 week and record in the provided activity diary as explained. I will then send the ActiGraph back to the investigator by whatever means are most convenient for me.	YES ☐	NO ☐
I am aware of the risks involved in this study that were outlined in the information leaflet. I have been made aware of what will happen in the case of a data breach. I am aware of the benefits and alternatives of this research study.	YES ☐	NO ☐
I confirm that I have read and fully understood the relevant Participant Information Leaflet (version 2, 17th June 2019) provided to me.	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I have received enough information about this study and understand what is involved if I agree to participate.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason with no consequence.	YES ☐	NO ☐
I agree to be contacted by researchers as part of this study.	YES ☐	NO ☐
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study.	YES ☐	NO ☐

Participant's Name (Block Capitals):		
Participant's Signature:		Date:

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher's Name (Block Capitals):		
Researcher's Title & Qualifications:		
Researcher's Signature:		Date:

***You are now entering a separate part of this consent form relating to data protection*.**

PART 2 – EXPLICIT, INFORMED CONSENT REGARDING DATA PROTECTION.

I understand that all of my data will be pseudonymised, minimised and subsequently anonymised for this study "The Irish Personalized Approach to the Treatment of Haemophilia (iPATH): An investigation of the relationship between physical health, physical activity and bleeding phenotype in adults with haemophilia in Ireland." The words pseudonymisation, minimisation and anonymisation have been explained to me.	YES □	NO □
I understand my name or other personal identifiers will not be disclosed to anybody not involved with this study and my personal data will be kept strictly confidential.	YES □	NO □
I understand the study investigators will be processing my data and the Lead Investigator in conjunction with Trinity College Dublin and St. James's Hospital is in control of my data.	YES □	NO □
I understand that my data will be used for comparative analysis with a clinical population group, published in peer reviewed journals, in presentations and may be disseminated at conferences but my data will remain confidential and none of my personal identifiers will be disclosed in these circumstances.	YES □	NO □

I understand how my data will be stored (pseudonymised, minimised and subsequently anonymised in secure locations only accessible to the research team) and that it will be stored for a total of 10 years and will then be securely destroyed by the study investigators.	YES □	NO □
I have been made aware of my rights under the General Data Protection Regulations and contact details of the Data Protection Officer and Data Commissioner have been provided to me in the Participant Information Leaflet.	YES □	NO □
I have read and understood the personal data protection section of the Participant Information Leaflet (version 2, 17th June 2019).	YES □	NO □
I have had the opportunity to discuss data protection in this study and I have received satisfactory answers to all my questions.	YES □	NO □
I understand that I am free to withdraw from the study at any time without giving a reason with no consequence and my personal data will not be used and will be securely destroyed.	YES □	NO □
I freely and voluntarily consent to allow the researcher's use of my information (personal data) as part of this study as outlined in the information leaflet and for my data to be pseudonymised, subsequently anonymised and archived to 10 years as specified in the Participant Information Leaflet.	YES □	NO □
I give my explicit consent to have my data processed as part of this research study	YES □	NO □

Participant's Name (Block Capitals):		
Participant's Signature:		Date:

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature of data protection in this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES □	NO □
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES □	NO □

Researcher's Name (Block Capitals):		
Researcher's Title & Qualifications:		
Researcher's Signature:		Date:

Appendix X: ActiGraph participant information leaflet

ActiGraph Activity Monitor Participant Information

Thank you for agreeing to wear the ActiGraph Activity Monitor. The ActiGraph measures your physical activity levels and provides us with information on the about of time you spend engaging in different intensities of activity. The following information leaflet addresses some frequently asked questions. Should you have any queries please contact the Physiotherapy Postgraduate and Research Room at the Trinity Centre for Health Sciences, St. James's Hospital on 01-8963613.

1. How many days do I wear the monitor?

You are requested to wear the activity monitor for one week (7 days) during waking hours.

2. Do I wear the monitor to bed?

No. You put the monitor on first thing in the morning and take it off last thing at night. You are requested to record the time you put the monitor on in the morning and the time you take if off at night in the activity diary provided.

3. Do I wear the monitor in the shower?

No. You should remove the monitor during any water-based activity such as showering, bathing or swimming. You are requested to record these activities, including the times you take the monitor on and off in the activity diary provided.

4. Do I need to press any button to start / finish the monitor?

No. The monitor is set-up by the researcher leading your study. You do not have to press any button to activate or stop the monitor.

5. Where on my body is the monitor worn?

The monitor is connected to a flexible strap with a clip. The strap should be worn like a belt around your waist with the monitor sitting at hip level on the right side of your body (see picture). Ensure the black disk on the side of the monitor is pointing towards your head. The strap should not be too tight or too loose. You can adjust the strap size if necessary. You may wear the monitor under or over your clothes.

Ensure this black disk is facing up towards you head.

6. Do I need to charge the monitor during the week?

No. Do not plug the monitor into any power source or connect to any USB cable during the week and this may wipe the data collected.

7. I forgot to wear the monitor – what should I do?

If you forget to wear the activity monitor on a particular day don't worry. Please write down clearly in the activity diary which day you forgot to wear the monitor and just carry on wearing it as normal the following day.

8. What should I do when I finish wearing the activity monitor?

When you finish wearing the monitor please return it to us in the stamped addressed envelope provided by post or in person at the centre. Please return the monitor to us as soon as possible to ensure that the battery does not die before we receive it.

Try not to change your activity levels while wearing the monitor as our aim is to get an idea of <u>normal</u> activity patterns

Thank you very much for recording your physical activity

Appendix XI: Physical activity diary

Physical Activity Diary

You are requested to wear your ActiGraph Activity Monitor during **all waking hours.** You will have to remove the activity monitor when you are going to bed or during water-based activities such as showering or swimming. Please record the time you put the activity monitor and the time you take it off in the following activity diary. This record will help us analyse your physical activity data as accurately as possible.

Should you have any further queries please contact Ms. Megan Kennedy at the Physiotherapy Postgraduate and Research Room at the Trinity Centre for Health Sciences, St. James's Hospital on 01-8963613.

Example activity diary:

On Date	On Time	Off Date	Off Time	Activity completed while not wearing monitor
04.10.2017	8.20am	04.10.2017	7.10pm	Shower
04.10.2017	7.30pm	04.10.2017	10.30pm	Sleeping in bed
05.10.2017	8.10am	05.10.2017	10.50pm	Sleeping in bed

Participants Study ID: _____

On Date	On Time	Off Time	Off Date	Activity completed while not wearing the monitor

Thank you for recording your physical activity.

Appendix XII: The Modifiable Activity Questionnaire

Modifiable Activity Questionnaire

1. Please circle all activities listed below that you have done more than 10 times in the past year.

01 Jogging (outdoor, treadmill)
02 Swimming (laps, snorkelling)
03 Bicycling (indoor, outdoor)
04 Softball/Baseball
05 Volley Ball
06 Bowling
07 Basketball
08 Skating
09 Martial Arts (karate, judo)
10 Tai chi
11 Calisthenics/Toning exercises
12 Wood Chopping
13 Water/coal hauling
14 Walking for exercise (outdoor/ indoor, treadmill)
15 Football/Soccer
16 Racquetball/Handball/Squash
17 Horseback riding
18 Hunting
19 Fishing
20 Aerobic Dance/Step Aerobic
21 Water Aerobics
22 Dancing (Square, Line, Ballroom)
23 Gardening or Yard work
24 Badminton
25 Strength/Weight training
26 Rock Climbing
27 Scuba Diving
28 Stair Master
29 Fencing
30 Hiking
31 Tennis
32 Golf
33 Canoeing
34 Water skiing
35 Jumping Rope
36 Snow skiing (X-country)
37 Snow skiing (Downhill)
38 Snow shoeing
39 Yoga/ Pilates
40 Rugby
41 Gaelic football
42 Hurling
43 Gym (cardio/ resistance training)
44 High Intensity Interval Training
45 Other: _____

List each activity that you circled in the "Activity" box below, check the months you did each activity over the past year (12 months) and then estimate the average amount of time spent in that activity.

Activity	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Average # of Times Per Month	Average # of Minutes Each Time

2. **In general, how many HOURS per DAY do you usually spend watching television? _____hours**

3. **What treatment regimen are you currently undertaking? Regular prophylaxis/ "On demand" treatment/ other? _____**

4. **At what age did you commence your current treatment regimen? What treatment did you take during childhood? _____**

5. **Do you take additional clotting factor concentrate before partaking in physical activity/ sport? If yes, how much? _____**

6. **Did you play sport/ exercise as a child/ adolescent? If yes, please specify/ If not, please provide reason why? _____**

Appendix XIII: The Borg Scale

Rating	Perceived Exertion
6	No exertion
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Appendix XIV: The Patient Reported Outcomes Burdens and Experiences Questionnaire (PROBE)

The Irish Haemophilia Society and the Patient Reported Outcomes Burdens and Experiences (PROBE) study group invite you to participate in a multinational, patient-focused research study to investigate and directly probe patient perspectives on outcomes that affect your own life and care.

We are seeking input from both individuals living with haemophilia as well as those who do not personally have a bleeding disorder. The research will support advocacy to improve care for people living with haemophilia. We appreciate your willingness to participate in this survey. The survey will take approximately 15 minutes to complete. You will be asked personal questions about your health, your age, your medical history and its impact on your daily living.

The PROBE study group would like to assure you that your responses to survey questions will not be connected to you individually. All responses will have identifying information removed and be combined with those from other respondents. A summary report will be provided to NHF.

The PROBE study is conducted by a global team of investigators with collaboration of the U.S. National Hemophilia Foundation. Should you have any questions about the study, you may contact the study team at PROBE@hemophilia.org or your local patient organisation (01 6579900, info@haemophilia.ie).

PERSONAL

1. Country you live in: _____

2. Gender:
   - ☐ Female
   - ☐ Male

3. Please select the category that best represents you personally.
   - ☐ Haemophilia A (FVIII). **Please proceed.**
   - ☐ Haemophilia B (FIX). **Please proceed.**
   - ☐ Carrier of haemophilia A or B. **Please proceed.**
   - ☐ I have a bleeding disorder other than haemophilia. **Please stop**. Thank you for your interest. However, you do not qualify to participate in this survey. Future research will address other bleeding disorders.
   - ☐ I am not a carrier, do not personally have haemophilia nor do I have any other bleeding disorder. **Please proceed.** The responses of individuals without a bleeding disorder are very important to our

research analysis. Please answer the questions for yourself if you are a parent or caregiver of a child with a bleeding disorder. Do not answer for your child.

4. Year of Birth: _____

5. Weight in kilograms (Kg): _____ or weight in stones and pounds (stones, lbs.): _____

6. How old were you when you first started school? Please fill in the blank: _____

How many years of school/education have you completed (include years studying for a vocational, professional or advanced degree)? Please fill in the blank: _____

7. Are you married or in a long-term relationship?

☐ Yes
☐ No

Do you have children?

☐ Yes
☐ No

PROBLEMS

8. In the past 12 months, have you experienced any problems related to your health?

☐ Yes
☐ No

If yes, please list your top 3 problems in order of seriousness:

_____

_____

_____

9. In the past 12 months, did you use a mobility aid or assistive device?

☐ Yes
☐ No

If yes, please indicate the frequency you used each of the following mobility aids or assistive devices in the past 12 months.

	Never (0% of the time)	Rarely (1–5% of the time)	Occasionally (6-25% of the time)	Sometimes (26–50% of the time)	Frequently (51–75% of the time)	Very Frequently (76-99% of the time)	Always (100% of the time)
Compression bandage/wrap	☐	☐	☐	☐	☐	☐	☐
Orthopaedic brace	☐	☐	☐	☐	☐	☐	☐
Orthotic shoes or inserts	☐	☐	☐	☐	☐	☐	☐
Sling	☐	☐	☐	☐	☐	☐	☐
Walking stick	☐	☐	☐	☐	☐	☐	☐
Crutches	☐	☐	☐	☐	☐	☐	☐
Walker	☐	☐	☐	☐	☐	☐	☐
Manual wheelchair	☐	☐	☐	☐	☐	☐	☐
Motorised wheelchair	☐	☐	☐	☐	☐	☐	☐
Electric scooter	☐	☐	☐	☐	☐	☐	☐
Other (Describe): _____	☐	☐	☐	☐	☐	☐	☐

10. During the <u>past 12 months</u> did you use <u>any</u> medication for pain?

- ☐ Yes
- ☐ No

If yes, please estimate the percent of the time you used pain medication.

- ❑ Rarely (1–5% of the time)
- ❑ Occasionally (6–25% of the time)
- ❑ Sometimes (26%–50% of the time)
- ❑ Frequently (51%–75% of the time)
- ❑ Very frequently (76%–99% of the time)
- ❑ All of the time (100% of the time)

11. “Acute pain” is defined as pain that arises in response to an event (like an injury or bleeding episode). “Acute pain” does not include “chronic pain.” “Chronic pain” is defined as pain from a persistent cause; it can vary in frequency and

intensity (like back pain, pain from sore joints, or arthropathy). During the past 12 months, have you experienced acute pain?

☐ Yes
☐ No

If yes, when did your acute pain occur? (Please check all that apply.)

☐ Walking
☐ Stair climbing
☐ At night (such as waking you up/keeping you awake)
☐ Resting
☐ Weight bearing
☐ Playing (including playing with children) or participating in sports / exercising
☐ After falling or a trauma
☐ Other (Describe): _____

If yes, did your acute pain interfere with any of the following? (Please check all that apply.)

☐ General activity
☐ Mood
☐ Walking ability
☐ Normal work (including both work outside the home and housework)
☐ Attending school
☐ Relations with others
☐ Sleep
☐ Enjoyment of life
☐ Playing (including playing with children) or participating in sports / exercising Lifting
☐ Other (Describe): _____

12. “Chronic pain” is defined as pain from a persistent cause; it can vary in frequency and intensity (like back pain, pain from sore joints, or arthropathy). “Chronic pain” does not include “acute pain.” “Acute pain” is defined as pain that arises in response to an event (like an injury or bleeding episode). During the past 12 months, have you experienced chronic pain?

☐ Yes
☐ No

If yes, when does your chronic pain occur? (Please check all that apply.)

☐ Walking
☐ Stair climbing
☐ At night (such as waking you up/keeping you awake)
☐ Resting
☐ Weight bearing
☐ Playing (including playing with children) or participating in sports / exercising
☐ After falling or a trauma
☐ Other (Describe): _____

If yes, does your chronic pain interfere with any of the following? (Please check all that apply.)
 General activity

☐Mood
☐Walking ability
☐Normal work (including both work outside the home and housework)
☐Attending school
☐Relations with others
☐Sleep
☐Enjoyment of life
☐Playing (including playing with children) or participating in sports / exercising Lifting
☐Other (Describe): _____

13. Do you currently have difficulty with any activities of daily living?
☐Yes
☐No

If yes, please check all that apply:
Getting out of bed

☐Bending down to the floor
☐Putting on socks or shoes
☐Getting up from sitting
☐Getting on or off the toilet
☐Taking a bath or shower
☐Brushing or flossing teeth
☐Grooming
☐Going down stairs
☐Sitting
☐Getting in or out of the car
☐Walking on a flat surface
☐Shopping
☐Playing (including playing with children) or participating in sports / exercising
☐Lifting light items
☐Standing without support
☐Writing or using a computer
☐Doing light domestic tasks
☐Doing heavy domestic tasks
☐Going up stairs
☐Taking off socks or shoes
☐Lying comfortably in bed
☐Sexual intimacy
☐Other (Describe): _____

14. Please select the answer that best describes your current work or school life.
☐Working full-time
☐Working part-time (Estimate percent of full-time: _____ %) If you are working part-time, is this due to your health?
☐Yes
☐No
☐Student full-time
☐Student part-time

If you are a student part-time, is this due to your health?

- ☐ Yes
- ☐ No
- ☐ On long-term sick or disability leave (more than 6 months)
- ☐ Unemployed
- ☐ Retired

If you retired early (prior to normal retirement age), was this due to your health?

- ☐ Yes
- ☐ No
- ☐ Stay-at-home parent or caregiver
- ☐ Other (Describe): _____

How many days during the past 12 months were you not able to work or attend school due to healthrelated reasons? _____

Have you made career decisions or choices due to your health?

- ☐ Yes
- ☐ No

15. Have you ever gone through joint surgery or another invasive procedure?

- ☐ Yes
- ☐ No

If yes, please check all that apply:

- ☐ Aspiration
- ☐ Amputation
- ☐ Arthroscopy
- ☐ Caesarean Section (C-section)
- ☐ Hysterectomy
- ☐ Joint replacement (arthroplasty)
- ☐ Joint fusion (arthrodesis)
- ☐ Radio or chemical synovectomy
- ☐ Surgical synovectomy
- ☐ Surgery for removal of a pseudotumour
- ☐ Other (Please describe): _____

If yes, how many joint surgeries or other invasive procedures have you ever gone through?

- ☐ 0
- ☐ 1
- ☐ 2-3
- ☐ 4-7
- ☐ 8-10
- ☐ More than 10

16. In the past 12 months have you had any of the following conditions or problems? (Please check all that apply)

Health problem or condition	Yes	No	Do not know	Prefer not to answer
Hepatitis B	☐	☐	☐	☐
Stroke / Brain haemorrhage	☐	☐	☐	☐
High blood pressure	☐	☐	☐	☐
Angina / Chest pain	☐	☐	☐	☐
Heart attack	☐	☐	☐	☐
Heart failure or enlarged heart	☐	☐	☐	☐
Asthma	☐	☐	☐	☐
Liver cancer	☐	☐	☐	☐
Cancer (other than liver)	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐
Seizure disorder	☐	☐	☐	☐
Arthritis	☐	☐	☐	☐
Gingivitis or gum disease (Bleeding gums)	☐	☐	☐	☐
HIV / AIDS	☐	☐	☐	☐
Renal / Kidney disease	☐	☐	☐	☐
Anxiety disorder	☐	☐	☐	☐
Clinically diagnosed depression	☐	☐	☐	☐
Other major health problems Specify_____	☐	☐	☐	☐

Have you ever been diagnosed with chronic (long-term) hepatitis C virus infection (HCV)?

- ☐ Yes
- ☐ No
- ☐ I do not know
- ☐ Prefer not to answer

If yes, please check the answer that best describes your current HCV status.

- ☐ I have cleared HCV spontaneously
- ☐ I have cleared HCV after treatment

☐I have been treated but the treatment was not successful in clearing my HCV.
☐I have not been treated.
☐I do not know my HCV status

HAEMOPHILIA-RELATED QUESTIONS

IF YOU DO NOT PERSONALLY HAVE HAEMOPHILIA, PLEASE SKIP TO QUESTION 29. THE FOLLOWING SECTION IS ONLY TO BE COMPLETED DIRECTLY BY PATIENTS THEMSELVES.
PARENTS AND CAREGIVERS SHOULD NOT COMPLETE THIS SECTION FOR THEIR CHILDREN.

17. How severe is your Haemophilia?
☐Severe (Factor level below 1%)
☐Moderate (Factor level 1-5%)
☐Mild (Factor level above 5-40%)
☐Normal factor level
☐I do not know

18. A "clinically significant" inhibitor is defined as not responding to normal treatment. Have you ever been diagnosed with a clinically significant inhibitor?
☐Yes
☐No
☐I do not know

If yes, do you currently have a clinically significant inhibitor?

☐Yes
☐No
☐I do not know

19. How many bleeds did you have in the past 12 months?
☐0 bleeds
☐1 bleed
☐2-3 bleeds
☐4-7 bleeds
☐8-10 bleeds
☐11-15 bleeds
☐16-30 bleeds
☐More than 30 bleeds

20. Within the past two weeks, have you had a bleed?
☐Yes
☐No

If yes, please describe: _____

21. What is your primary treatment regimen? (Check one answer that best describes your current regimen.)

☐ Regular prophylaxis (Regular, continuous treatment to prevent bleeds with an intent to treat for 52 weeks of the year)

☐ Intermittent, "periodic" prophylaxis (Treatment given to prevent bleeding before a specific activity or for short periods of time, not more than 45 weeks in a year)

☐ Episodic ("on-demand") (Treatment given at the time of clinically evident bleeding)

☐ Immune tolerance induction (ITI) (Treatment to overcome an inhibitor)

☐ No treatment available

22. How do you currently treat? If you treat with a combination of regimens, please indicate all that apply.

Prophylaxis (Regular or Intermittent) with Factor Concentrate	**Episodic ("On-Demand") with Factor Concentrate**	**Other Treatment**
Typical dose of Factor VIII/IX concentrate used. Please indicate IUs per infusion: _____	Typical dose of Factor VIII/IX concentrate used per infusion. Please indicate IUs per infusion: _____	You use products other than Factor VIII/IX concentrates: ☐ Whole blood transfusions ☐ Fresh-frozen plasma ☐ Cryoprecipitate ☐ Antifibrinolytics (e.g., tranexamic acid or aminocaproic acid) ☐ Desmopressin (DDAVP) ☐ Bypassing agents ☐ Other therapies (Please describe): _____
Typical prophylaxis frequency: ☐ Daily ☐ Every other day ☐ 3 times per week ☐ 2 times per week ☐ Once per week ☐ Other (Please describe): _____	Number of infusions typically required to treat a bleeding episode: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ More than 5	
Do you currently use an extended (prolonged) half-life treatment product? ☐ Yes ☐ No	Do you currently use an extended (prolonged) half-life treatment product? ☐ Yes ☐ No	

Where do you usually receive your prophylaxis treatment? ☐ Home ☐ Haemophilia treatment centre (HTC) ☐ Emergency room ☐ Other (Please specify): _____ ☐ No treatment available	Where do you usually receive your episodic treatment? ☐ Home ☐ Haemophilia treatment centre (HTC) ☐ Emergency room ☐ Other (Please specify): _____ ☐ No treatment available	

23. Please give a brief history of your treatment regimens during your lifetime. (Provide your best estimate or approximate age.)

	From Age	To Age	Treatment regime
Example	0	2	No treatment
Example	2	3	Episodic (on demand)
Example	4	5	Immune tolerance
Example	6	21	Regular prophylaxis
Example	22	39	Episodic (on demand)
1			
2			
3			
4			
5			
6			
7			

24. Do you currently have any “target joints”?

☐ Yes

☐No
☐I do not know

If yes, which joint(s)? (Please check all that apply.)

☐Left ankle
☐Right ankle
☐Left elbow
☐Right elbow
☐Left knee
☐Right knee
☐Other (Describe): _____

Are any of these joints causing you “chronic pain”?

☐Yes
☐No

25. Have you had 3 or more spontaneous bleeds (including those resulting from normal daily activity) into any one joint in the past 6 months?

☐Yes
☐No
☐I do not know

26. Is the range of motion of any joint currently reduced because of your having haemophilia?

☐Yes
☐No

If yes, which joint(s)? (Please check all that apply.)

☐Left ankle
☐Right ankle
☐Left elbow
☐Right elbow
☐Left knee
☐Right knee
☐Other (Describe): _____

27. Other than joint bleeds, have you had any life- or limb-threatening bleeds in the past 12 months?

☐Yes
☐No

If yes, please check all that apply:

☐Calf
☐Dental
☐Forearm
☐Gastrointestinal
☐Head/ intracranial haemorrhage (ICH)
☐Iliopsoas
☐Internal organ (e.g., kidney, liver) □ Bleeding related to childbirth

☐ Bleeding related to menstruation
☐ Bleeding related to surgery
☐ Other (Please describe):
_____

29. Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

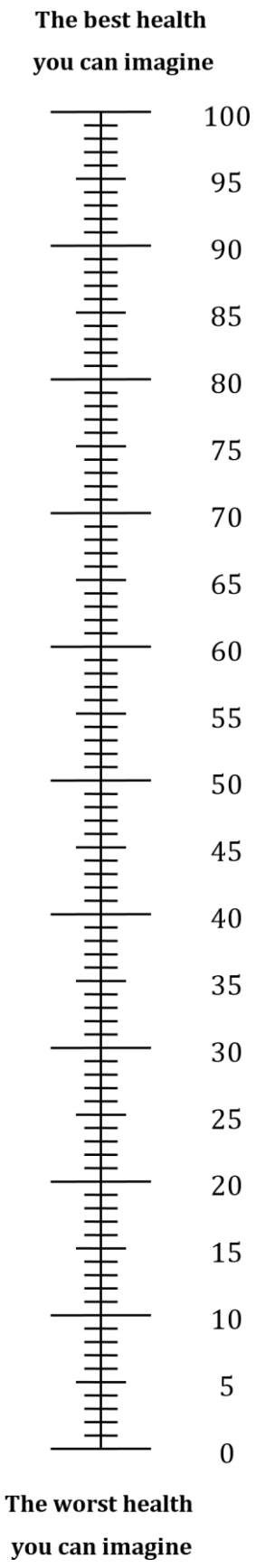
We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.

0 means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY [ ] =



Appendix XV: The Barriers to Being Active Quiz

Barriers to Being Active Quiz
What keeps you from being more active?

Directions: Listed below are reasons that people give to describe why they do not get as much physical activity as they think they should. Please read each statement and indicate how likely you are to say each of the following statements:

How likely are you to say?	Very likely	Somewhat likely	Somewhat unlikely	Very unlikely
1. My day is so busy now, I just don't think I can make the time to include physical activity in my regular schedule.	3	2	1	0
2. None of my family members or friends like to do anything active, so I don't have a chance to exercise.	3	2	1	0
3. I'm just too tired after work to get any exercise.	3	2	1	0
4. I've been thinking about getting more exercise, but I just can't seem to get started	3	2	1	0
5. I'm getting older so exercise can be risky.	3	2	1	0
6. I don't get enough exercise because I have never learned the skills for any sport.	3	2	1	0
7. I don't have access to jogging trails, swimming pools, bike paths, etc.	3	2	1	0
8. Physical activity takes too much time away from other commitments—time, work, family, etc.	3	2	1	0
9. I'm embarrassed about how I will look when I exercise with others.	3	2	1	0

10. I don't get enough sleep as it is. I just couldn't get up early or stay up late to get some exercise.	3	2	1	0

11. It's easier for me to find excuses not to exercise than to go out to do something.	3	2	1	0
12. I know of too many people who have hurt themselves by overdoing it with exercise.	3	2	1	0
13. I really can't see learning a new sport at my age.	3	2	1	0
14. It's just too expensive. You have to take a class or join a club or buy the right equipment.	3	2	1	0
15. My free times during the day are too short to include exercise.	3	2	1	0
16. My usual social activities with family or friends to not include	3	2	1	0
physical activity.				
17. I'm too tired during the week and I need the weekend to catch up on my rest.	3	2	1	0
18. I want to get more exercise, but I just can't seem to make myself stick to anything.	3	2	1	0
19. I'm afraid I might injure myself or have a heart attack.	3	2	1	0
20. I'm not good enough at any physical activity to make it fun.	3	2	1	0
21. If we had exercise facilities and showers at work, then I would be more likely to exercise.	3	2	1	0

Follow these instructions to score yourself:

- Enter the circled number in the spaces provided, putting together the number for statement 1 on line 1, statement 2 on line 2, and so on.
- Add the three scores on each line. Your barriers to physical activity fall into one or more of seven categories: lack of time, social influences, lack of energy, lack of willpower, fear of injury, lack of skill, and lack of resources. A score of 5 or above in any category shows that this is an important barrier for you to overcome.

1	____ +	8 ____ +	15 ____ =	_____	Lack of time
2	____ +	9 ____ +	16 ____ =	_____	Social influence
3	____ +	10 ____ +	17 ____ =	_____	Lack of energy
4	____ +	11 ____ +	18 ____ =	_____	Lack of willpower
5	____ +	12 ____ +	19 ____ =	_____	Fear of injury
6	____ +	13 ____ +	20 ____ =	_____	Lack of skill
7	____ +	14 ____ +	21 ____ =	_____	Lack of resources

Appendix XVI: Longitudinal follow-up questionnaire for Study IV

"A Follow-up of Physical Activity and Quality of Life in Adults with Haemophilia in Ireland from the iPATH Study."

Dear Participant,

As you are aware, we are interested to know if your physical activity habits have changed in the past year and if the Covid-19 pandemic had any impact on your physical activity and health. This questionnaire involves a series of questions related to physical activity and other aspects of quality of life during the past year and during the pandemic.

Completion of this questionnaire is optional and if you choose not to complete it, it will not impact on your care.

Please provide as much detail as you can recall and answer these questions as honestly as possible.

If you have any queries regarding this questionnaire, please contact the iPATH Physiotherapist, Megan Kennedy by Email: kennedme@tcd.ie or Phone: 01-8963613.

1. What is your current treatment regimen?

Regular prophylaxis ☐

On demand ☐

Other ☐ Please specify: _____

Please specify the following: Product name: _____

Dosage: _____

2. At what age did you commence your current treatment regimen?

_____

3. Did your participation in the iPATH Physical Activity Study make you more aware of your physical activity habits?

A lot more aware ☐

Somewhat more aware ☐

My awareness did not change ☐

Somewhat less aware ☐

A lot less aware ☐

4. Please complete the following sentence:

"My participation in the iPATH Physical Activity Study made me want to…"

Become a lot more physically active ☐

Become somewhat more physically active ☐

Maintain my current physical activity levels ☐

Become somewhat less physically active ☐

Become a lot less physically active ☐

5. Have you participated in any new exercise programme or sport in the past year? If yes, please specify.

Yes ☐ If yes, please specify: _____

No ☐

6. Do you know how much physical activity adults are recommended to undertake as per the global guidelines? If yes, please state.

_____

7. Please circle all activities listed below that you have done more than 10 times in the past year.

01 Jogging (outdoor, treadmill)
02 Swimming (laps, snorkelling)
03 Bicycling (indoor, outdoor)
04 Softball/Baseball
05 Volley Ball
06 Bowling
07 Basketball
08 Skating
09 Martial Arts (karate, judo)
10 Tai chi
11 Calisthenics/Toning exercises
12 Wood Chopping
13 Water/coal hauling
14 Walking for exercise (outdoor/ indoor, treadmill)
15 Football/Soccer
16 Racquetball/Handball/Squash
17 Horseback riding
18 Hunting
19 Fishing
20 Aerobic Dance/Step Aerobics
21 Water Aerobics
22 Dancing (Square, Line, Ballroom)
23 Gardening or Yard work
24 Badminton
25 Strength/Weight training
26 Rock Climbing
27 Scuba Diving
28 Stair Master
29 Fencing
30 Hiking
31 Tennis
32 Golf
33 Canoeing
34 Water skiing
35 Jumping Rope
36 Snow skiing (X-country)
37 Snow skiing (Downhill)
38 Snow shoeing
39 Yoga/ Pilates
40 Rugby
41 Gaelic football
42 Hurling
43 Gym (cardio/ resistance)
44 HIIT
45 Other: _____

List each activity that you circled in the "Activity" box below, tick the months you did each activity over the past year (12 months) and then estimate the average amount of time spent in that activity.

Activity	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	Average # of Times Per Month	Average # of Minutes Each Time

8. Were you diagnosed with Covid-19 in the past year?

Yes ☐ No ☐

9. Was any person living in your household diagnosed with Covid-19 in the past year?

Yes ☐ No ☐

10. If yes, when were you ill and how long did it take you to recover (approximate dates)?

_____

11. If yes, were you admitted to hospital?

_____

12. During the first full lockdown, when non-essential travel was advised against and exercise was only allowed within a 2km radius from your home (March 27th- May 5th 2020), how was your physical activity <u>compared to normal</u>?

A lot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active ☐

A lot

more active ☐

13. During the first partial lockdown, when non-essential travel was advised against and exercise was only allowed within a 5km radius from your home (May 5th- May 18th 2020), how was your physical activity compared to normal?

A lot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active ☐

A lot more active ☐

14. During the initial phased re-opening of the country (May 18th 2020 until restrictions were tightened again in your county during the second wave of the pandemic), how was your physical activity compared to normal?

A lot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active ☐

A lot more active ☐

15. During the second national lockdown (Oct 21st- Dec 1st 2020), how was your physical activity compared to normal?

Alot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active☐

A lot more active ☐

16. During the second re-opening of the country during the run-up to Christmas (1st Dec- 26/30th Dec 2020), how was your physical activity compared to normal?

A lot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active ☐

A lot more active ☐

17. During the third national lockdown (Dec 30th 2020- Apr 12th 2021), how was your physical activity compared to normal?

A lot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active ☐

A lot more active ☐

18. During the third phased re-opening of the country (Apr 12th 2021-present), how was your physical activity <u>compared to normal</u>?

A lot less active ☐

Somewhat less active ☐

No different ☐

Somewhat more active ☐

A lot more active ☐

Please tick the box beside the answer which applies to you:

19. Did you have any problems with your mobility during the lockdown period?

A lot more than normal ☐

Somewhat more than normal ☐

No different ☐

Somewhat less than normal ☐

A lot less than normal ☐

20. Did you have any problems with your usual activities of daily living (i.e. washing, dressing, grooming, work, housework, etc.) during the lockdown period?

A lot more than normal ☐

Somewhat more than normal ☐

No different ☐

Somewhat less than normal ☐

A lot less than normal ☐

21. Did you experience pain during the lockdown period?

A lot more than normal ☐

Somewhat more than normal ☐

No different ☐

Somewhat less than normal ☐

A lot less than normal ☐

22. What are your main concerns for physical activity in the next 12 months?

_____

_____

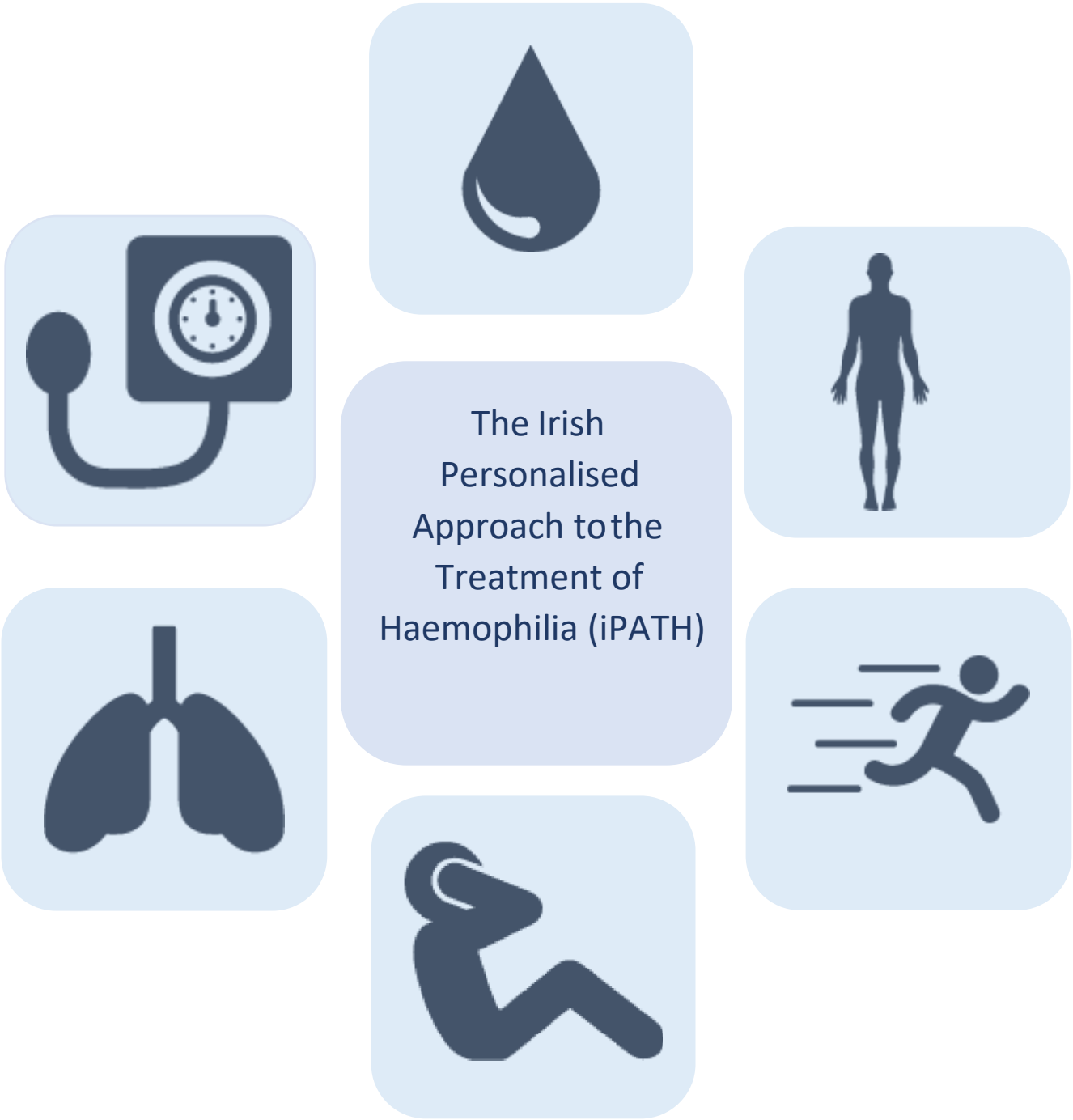
23. **Do you have any other comments about the impact of COVID-19 on your physical activity, functional ability or pain?**

_____

_____

This is the end of the questionnaire- Thank you very much for your participation.

Appendix XVII: Participant feedback report



Health and Activity Report

Participant ID

Thank you for your recent participation in the iPATH Physical Health and Activity study. The team

has analysed your data and compiled your results. As well as reporting your individual results, **the normal reference ranges for the general population are also indicated in a table to the right of your result**. These are specific to your age and gender. You can find where your results fall within
these ranges to establish your health status for each component of the assessment.

Being more physically active can greatly improve overall health. Regular daily physical activity (30 minutes or more) can reduce the risk of heart disease, high blood pressure, diabetes and can

improve levels of mood and fatigue.

If you have further queries about these results, please feel free to consult with your medical team.

Date of assessment:

Height (cm):

Weight (kg):

Compiled by:

Megan Kennedy BSc MISCP
Chartered Physiotherapist

Email: kennedme@tcd.ie| Tel: 01-8963613

Blood Pressure

Ideal average blood pressure, (also known sometimes as BP), is typically, around 120/80. The first number, always the higher number, is the pressure in the blood vessels when the heart is beating and the lower number is the pressure in -between beats, when t he heart is relaxed. High blood pressure is generally accepted as being **persistently** over 140/90 according to medical guidelines. High blood pressure is associated with an increased risk of developing heart disease.

Blood Pressure

Your result

Low	<90/60
Normal	120/80
Increased	140/90 +

Body Composition

Body fat is vital to daily body function. However, it is not the amount you weigh but your percentage body fat that potentially influences your health. Weight alone does not distinguish between fat and lean body tissue (muscle and bone). If you start exercising and don't appear to be losing weight, you may in fact be reducing your body fat and replacing it with newly developed muscle mass, which is denser and heavier than fat. Excessive body fat can increase your risk of developing serious health problems such as high blood pressure, high cholesterol, heart disease, diabetes and cancer. Maintaining a healthy body fat percentage can reduce your risk and help prevent the onset of these conditions. Too little body fat can also be unhealthy.

BMI

Your Result

BMI (kg/m^2)

Underweight	< 18.5
Normal	18.5 - 24.9
Overweight	25.0 - 29.9
Obese	30 +

Waist Circumference

A **waist circumference** measurement is a good way to check your fat distribution. Carrying too much weight around your middle can increase your risk of developing many conditions including heart disease, high blood pressure and diabetes.

Your Result

Waist Circumference (*cm*)

Risk of complications associated with obesity:	
Not increased	< 80
Increased	≥ 94
Substantially increased	≥ 102

Waist– Hip Ratio

Waist-hip ratio measures how the above waist circumference measure relates you your hip circumference. This measure is a good predictor of risk of developing health problems associated with obesity

Your Result

Waist-Hip Ratio Index

Risk of complications associated with obesity	
Not Increased	<0.90
Increased	0.90+
Substantially increased	1.00+

Body fat %

Body fat is vital to daily body functions. It cushions joints, protects organs, helps regulate body temperature, and stores vitamins. However, serious health risks are associated with both too much, and too little body fat. By design, women's bodies require a higher percentage of body fat to be healthy.

Reference Range (%)

Age (yr)	Excellent	Good	Average	High	Obese
20-29	5 - 10	10.1 - 14	14.1 - 17	17.1 - 22	22.1+
30-39	6 - 14	14.1 - 18	18.1 - 21	21.1 - 24	24.1+
40-49	7 - 16	16.1 - 20	20.1 - 23	23.1 - 26	26.1 +
50-59	8 – 18	18.1- 21	21.1 - 24	24.1 - 28	28.1 +
60+	10 - 18	18.1 - 22	22.1 - 25	25.1 - 29	29.1 +

Body Fat Free Mass %.

Body Fat Free Mass % is everything in the body that is not fat; muscle, water, bone, connective tissue, etc. Muscle acts as the body's natural "fat -burning engine," therefore it is important to maintain or even gain healthy muscle mass when dieting or exercising.

Your Result

Body fat free mass (%)

Athletic	83 - 86
Normal	76 - 82
Increased Health Risk	0-75

Fat Mass Index

Fat Mass Index and Fat Free Mass Index are additional measures of body fat mass and fat free mass versus height.

A high Fat Mass Index is associated with increased risk of developing high blood pressure, heart disease or diabetes. For Fat Free Mass Index, a low measure indicates this risk is increased.

Your Result

Fat Mass Index

Age (yr)	Normal	Increased risk
18-34	3.2 – 5	5.1+
35-54	3.7 - 6	6.1+
55+	4.3 -7.6	7.8+

Fat Free Mass Index

Fat free mass index takes into account the amount of muscle mass a person is carrying and relates that to their height. It is not necessarily a superior index, but it does factor in different parameters than simply total weight.

Your Result

Fat Free Mass Index

Age (yr)	Increased Risk	Normal
18-34	<18	18.1- 19.8
35-54	<18.3	18.4 - 20.1
55+	<18.4	18.5 – 20.3

Physical Activity

Adults need **<u>at least</u> 150 minutes of *moderate-intensity* aerobic exercise** (e.g. brisk walking, riding a bike, pushing a lawn mower) **or 75 minutes of *vigorous-intensity* aerobic activity** (e.g. jogging or running, swimming lengths, or running) every week. Activities can be broken down into smaller chunks of time, as long as the activity is at least 10 minutes long.

Physical activity is a major modifiable risk factor for heart disease, stroke, type 2 diabetes and certain cancers. It is also associated with mental health and obesity. If you haven't been very active lately, increase your activity levels gradually.

In this study, we also measured your perception of physical activity levels via a questionnaire. Check to see how you compare with the results from the activity monitor data!

Weekly Physical Activity Recommendations

(Minimum 150 min moderate or 75 min vigorous physical activity)

	Your Result
Sedentary activity per week (Sleep excluded)	
Light-intensity (minutes per week)	
Moderate-intensity (minutes per week)	
Vigorous-intensity (minutes per week)	

Appendix XVIII: Total sample demographic statistics

Total haemophilia group demographics (categorical variables)

n= 54	Total n (%)	Severe FVIII n (%)	Severe FIX n (%)	Moderate FVIII n (%)	Moderate FIX n (%)
n (% of total)	54 (100)	32 (59.3)	15 (27.8)	6 (11.1)	1 (1.8)
Inhibitor history					
History of inhibitors (non-active)	7 (13.0)	6 (85.7)	1 (14.3)	0	0
No history of inhibitors	47 (87.0)	26 (55.3)	14 (29.8)	6 (12.8)	1 (2.1)
Treatment regimen					
On demand	6 (11.1)	-	-	5 (83.3)	1 (16.7)
Prophylaxis	48 (88.9)	32 (66.7)	15 (31.2)	1 (2.1)	-
Treatment product					
Standard half-life product	3 (6.3)	3 (100)	0	-	-
Extended half-life product	43 (89.5)	27 (62.8)	15 (34.9)	1 (2.3)	-
Non-factor replacement product	2 (4.2	2 (100)	-	-	-
History of chronic infectious disease					
Hepatitis-C Virus (previous history)	38 (70.4)	19 (50.0)	14 (36.8)	5 (13.2)	0
Hepatitis-C Virus (no history)	16 (29.6)	13 (81.3)	1 (6.2)	1 (6.2)	1 (6.2)
Human Immunodeficiency Virus (positive)	14 (25.9)	11 (78.6)	1 (7.1)	2 (14.3)	0
Human Immunodeficiency Virus (negative)	40 (74.1)	21 (52.5)	14 (35.0)	4 (10.0)	1 (2.5)
Orthopaedic surgical history					
Ankle arthrodesis	7 (13.0)	3 (42.9)	4 (57.1)	0	0
Total Knee Replacement	6 (11.1)	4 (66.7)	2 (33.3)	0	0
Total elbow replacement	1 (1.9)	1 (100)	0	0	0
Total Hip Replacement	1 (1.9)	0	1 (100)	0	0
Body Mass Index category					
Underweight	1 (1.9)	0	1 (100)	0	0
Normal	17 (31.5)	12 (70.6)	3 (17.6)	2 (11.8)	0
Overweight	23 (42.6)	13 (56.5)	7 (30.4)	2 (8.7)	1 (4.3)
Obese	13 (24.0)	7 (53.8)	4 (30.8)	2 (15.4)	0

Total haemophilia group demographics (continuous variables)

n=54	Mean ± SD	95% CI	Median (IQR:Q1, Q3)	Range (min-max)
Age (years)	42 ± 13	(38-45)	44 (19; 32, 51)	18-71
Age prophylaxis commenced (years)	27 ± 19	(21-33)	26 (36.5; 11.5, 48.0)	0-63
Anthropometry				
Height (cm)	175.6 ± 7.1	(173.6-177.5)	174.2 (12.2; 169.5, 181.7)	161.5-194.0
Weight (kg)	83.8 ± 16.0	(79.4-88.1)	83.8 (21.1; 72.5, 93.6)	51.9-131.7
BMI (kg/m^2)	27.1 ± 4.6	(25.9-28.4)	27.0 (5.4; 24.6, 30.1)	18.2-39.2
Joint Health (n-5 with moderate haemophilia)				
HJHS Total	27 ± 13	(23-31)	28 (14; 20, 34)	1-54
HJHS Elbow	8 ± 6	(6-9)	7 (11; 1, 12)	0-21
HJHS Knee	5 ± 6	(4-7)	4 (8; 1, 9)	0-21
HJHS ankle	11 ± 6	(9-12)	12 (7; 8, 15)	0-22
HJHS lower limb	16 ± 9	(13-18)	15 (9; 12, 21)	0-41
Global Gait Score	3 ± 1	(3-4)	4 (0; 4, 4)	0-4
Bleeding phenotype				
ABR (Bleeds per annum)	3 ± 3	(2-4)	2 (3; 1, 4)	0-14
AJBR (Joint bleeds per annum)	2 ± 2	(1-2)	1 (3; 0, 3)	0-11
Spontaneous bleeds	0 ± 1	(0-1)	0 (1; 0, 1)	0-2
Traumatic bleeds	1 ± 1	(0-1)	0 (1; 0, 1)	0-3
Unknown cause bleeds	2 ± 3	(1-3)	1 (3; 0, 3)	0-14
Clinically defined target joints	0	0	0	0
Clinically verified bleeds‡	0 ± 1	(0-1)	0 (0; 0, 0)	0-4

n= FVIII (38); FIX (16); Moderate (7); Severe (47); ABR Annualised Bleed Rate **AJBR** Annualised Joint Bleed Rate **BMI** Body Mass Index **CI** Confidence Interval **HJHS** Haemophilia Joint Health Score **IQR** Interquartile Range **max** Maximum **min** Minimum **SD** Standard Deviation ‡ based off n=42 participants who experienced bleeds, those who had 0 bleeds were excluded

Severe haemophilia A demographics (continuous variables)

n= 32	Mean ± SD	95% CI	Median (IQR:Q1, Q3)	Range (min-max)
Age (years)	39 ± 13	(34-43)	38 (22; 27, 49)	18-64
Age prophylaxis commenced (years)**	24 ± 19	(17-32)	22 (28; 11, 39)	0-63
Anthropometry				
Height (cm)	175.3 ± 7.0	(173.1-178.1)	175.7 (11.8; 170.0, 181.8)	161.5-187.2
Weight (kg)	83.2 ± 18.2	(76.6-89.8)	81.7 (26.2; 70.2, 96.4)	51.9-131.7
BMI (kg/m^2)	26.9 ± 4.9	(25.1-28.6)	26.6 (6.9; 22.7, 29.6)	19.2-39.2
Joint Health				
HJHS Total	27 ± 13	(22-32)	29 (17; 20, 37)	1-51
HJHS Elbow	9 ± 6	(6-11)	9 (10; 3, 13)	0-21
HJHS Knee	5 ± 5	(3-7)	4 (8; 0, 8)	0-18
HJHS ankle	10 ± 6	(8-12)	11 (8; 6, 14)	0-22
HJHS lower limb	15 ± 8	(12-18)	15 (9; 11, 20)	0-32
Global Gait Score	3 ± 1	(3-4)	4 (0; 4, 4)	0-4
Bleeding phenotype				
ABR (Bleeds per annum)	3 ± 3	(2-4)	2 (4; 0, 4)	0-14
AJBR (Joint bleeds per annum)	2 ± 2	(1-3)	1 (3; 0, 3)	0-11
Spontaneous bleeds	0 ± 1	(0-1)	0 (0; 0, 0)	0-2
Traumatic bleeds	0 ± 1	(0-1)	0 (1; 0, 1)	0-2
Unknown cause bleeds	2 ± 3	(1-3)	1 (3; 0, 3)	0-14
Clinically defined target joints	0	-	0	-
Clinically verified bleeds‡	0 ± 1	(0-4)	0 (0; 0, 0)	0-2

ABR Annualised Bleed Rate **AJBR** Annualised Joint Bleed Rate **BMI** Body Mass Index **CI** Confidence Interval **HJHS** Haemophilia Joint Health Score **IQR** Interquartile Range **max** Maximum **min** Minimum **SD** Standard Deviation ‡ based off n=24 participants who experienced bleeds, those who had 0 bleeds were excluded; **n= 28 as 4 participants did not answer question

Severe haemophilia B demographics (continuous variables)

n= 15	Mean ± SD	95% CI	Median (IQR:Q1, Q3)	Range (min-max)
Age (years)	47 ± 13	(40-54)	47 (13; 42, 55)	18-71
Age prophylaxis commenced (years)**	34 ± 18	(23-45)	38 (31; 20, 51)	2-55
Anthropometry				
Height (cm)	174.0 ± 5.0	(171.2-176.7)	172.4 (7.5; 169.3, 176.8)	168.4-183.4
Weight (kg)	83.0 ± 12.4	(76.1-89.9)	84.0 (13.8; 75.9, 89.7)	61.1-109.0
BMI (kg/m^2)	27.5 ± 3.9	(25.3-29.6)	28.3 (5.7; 24.9, 30.6)	18.2-32.7
Joint Health				
HJHS Total	28 ± 14	(21-36)	27 (13; 21, 34)	1-54
HJHS Elbow	6 ± 5	(3-9)	6 (8; 1, 9)	0-16
HJHS Knee	6 ± 6	(3-10)	4 (8; 2, 10)	0-21
HJHS ankle	12 ± 5	(10-15)	12 (5; 10, 15)	1-20
HJHS lower limb	19 ± 10	(13-24)	18 (7; 14, 21)	1-41
Global Gait Score	4 ± 1	(3-4)	4 (0; 4, 4)	0-4
Bleeding phenotype				
ABR (Bleeds per annum)	3 ± 4	(1-5)	2 (3; 1, 4)	0-12
AJBR (Joint bleeds per annum)	2 ± 2	(1-3)	1 (3; 0, 3)	0-8
Spontaneous bleeds	0 ± 1	(0-1)	0 (1; 0, 1)	0-2
Traumatic bleeds	1 ± 1	(0-1)	1 (1; 0, 1)	0-2
Unknown cause bleeds	2 ± 3	(0-4)	0 (3; 0, 3)	0-9
Clinically verified bleeds‡	0 ± 0	(0-0)	0 (0; 0, 0)	0-1

ABR Annualised Bleed Rate **AJBR** Annualised Joint Bleed Rate **BMI** Body Mass Index **CI** Confidence Interval **HJHS** Haemophilia Joint Health Score **IQR** Interquartile Range **max** Maximum **min** Minimum **SD** Standard Deviation ‡ based off n=13 participants who experienced bleeds, those who had 0 bleeds were excluded **n= 13 as 2 participants did not answer question

Moderate FVIII subgroup sample demographic descriptive statistics (continuous variables)

n= 6	Mean ± SD	95% CI	Median (IQR:Q1, Q3)	Range (min-max)
Age (years)	47 ± 13	(33-61)	50 (26; 33, 59)	29-63
Age prophylaxis commenced (years)**	7	-	-	-
Anthropometry				
Height (cm)	177.3 ± 11.1	(165.7-188.9)	175.9 (19.7; 167.2, 186.9)	166.1-194.0
Weight (kg)	85.4 ± 12.4	(72.4-98.5)	88.8 (23.2; 71.8, 95.0)	68.8-100.1
BMI (kg/m^2)	27.4 ± 5.5	(21.7-33.2)	25.8 (10.2; 23.6, 33.8)	20.2-34.2
Joint Health (n-4; HJHS only available for 2 participants)				
HJHS Total	12 ± 7	NA	12 (NA)	7-17
HJHS Elbow	1 ± 1	NA	1 (NA)	0-1
HJHS Knee	3 ± 3	NA	3 (NA)	1-5
HJHS ankle	5 ± 4	NA	5 (NA)	2-7
HJHS lower limb	8 ± 6	NA	8 (NA)	3-12
Global Gait Score	4 ± 0	NA	4 (NA)	4-4
Bleeding phenotype				
ABR (Bleeds per annum)	4 ± 3	(1-7)	4 (5; 2, 7)	0-7
AJBR (Joint bleeds per annum)	1 ± 2	(0-3)	1 (3; 0, 3)	0-3
Spontaneous bleeds	1 ± 1	(0-2)	2 (2; 0, 2)	0-2
Traumatic bleeds	1 ± 1	(0-2)	1 (2; 0, 2)	0-3
Unknown cause bleeds	2 ± 3	(-1-5)	1 (4; 0, 4)	0-7
Clinically defined target joints	0	0	0	0
Clinically verified bleeds‡	2 ± 2	(0-4)	1 (4; 0, 4)	0-4

ABR Annualised Bleed Rate **AJBR** Annualised Joint Bleed Rate **BMI** Body Mass Index **CI** Confidence Interval **HJHS** Haemophilia Joint Health Score **IQR** Interquartile Range **max** Maximum **min** Minimum **SD** Standard Deviation ‡ based off n=5 participants who experienced bleeds, those who had 0 bleeds were excluded ** only 1 participant with Moderate HA on prophylaxis, raw value reported

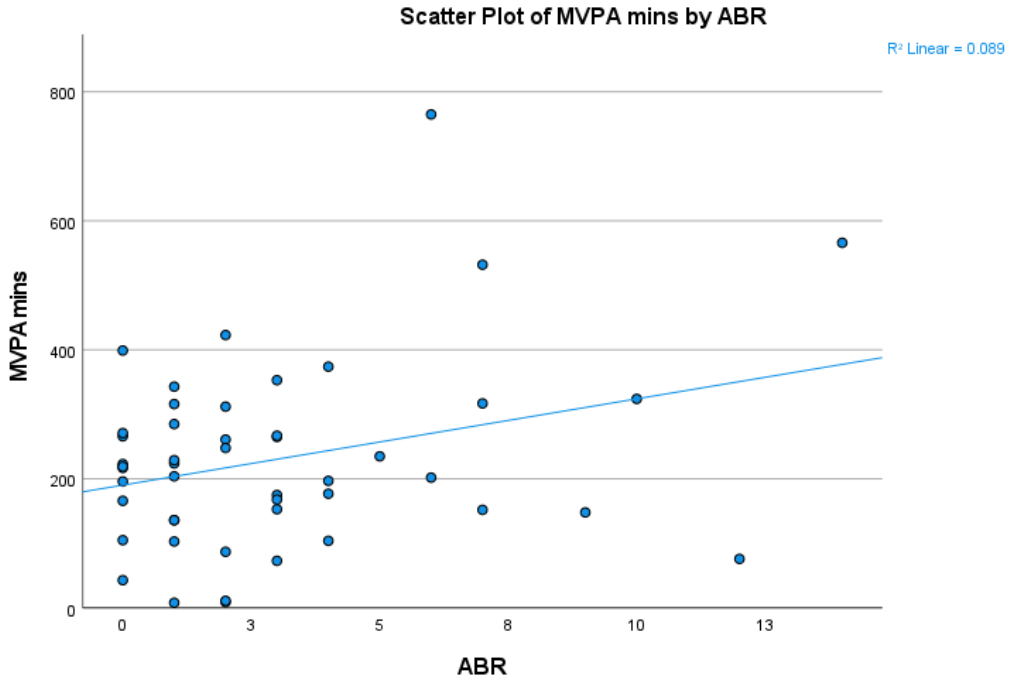
Moderate haemophilia B demographics (n=1); No available HJHS; Treated on demand; ABR= 0

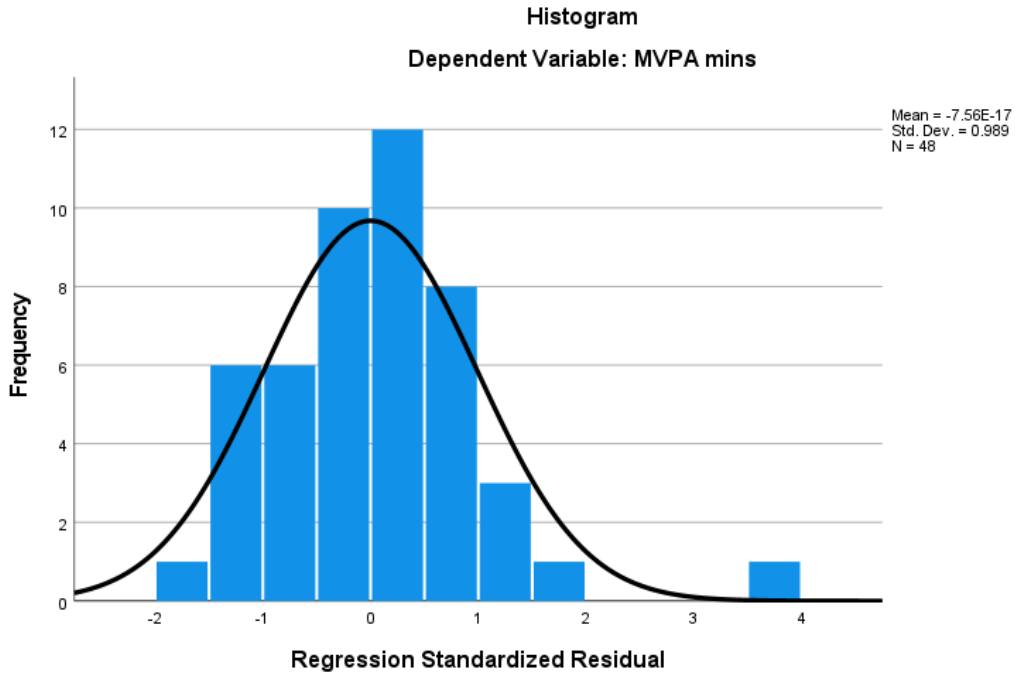
n=1	
Age (years)	32
Anthropometry	
Height (cm)	189.0
Weight (kg)	103.0
Body Mass Index (kg/m^2)	28.8

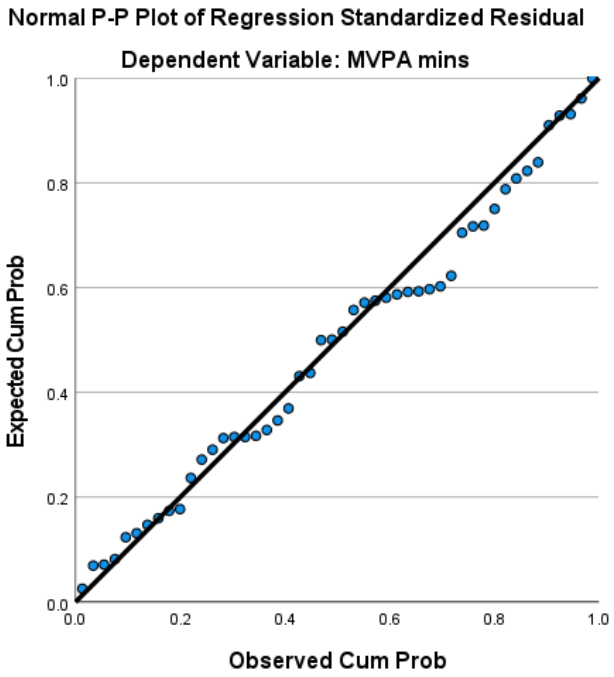
Total control group sample demographics (categorical variables)

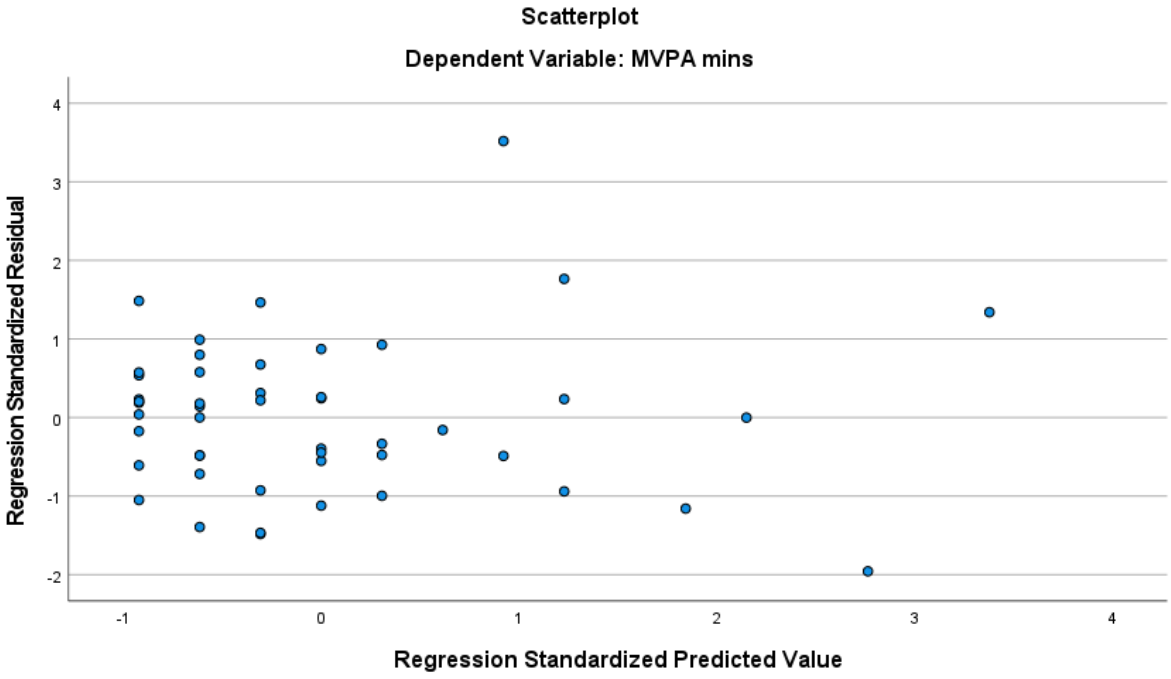
N	**33**
Body Mass Index category	**n (%)**
Underweight	0
Normal	16 (48.5)
Overweight	12 (36.4)
Obese	5 (15.2)

Appendix XIX: Residuals of Annualised Bleeding Rate (ABR) and Moderate-Vigorous Physical Activity (MVPA) (outlier included) (Chapter 3)

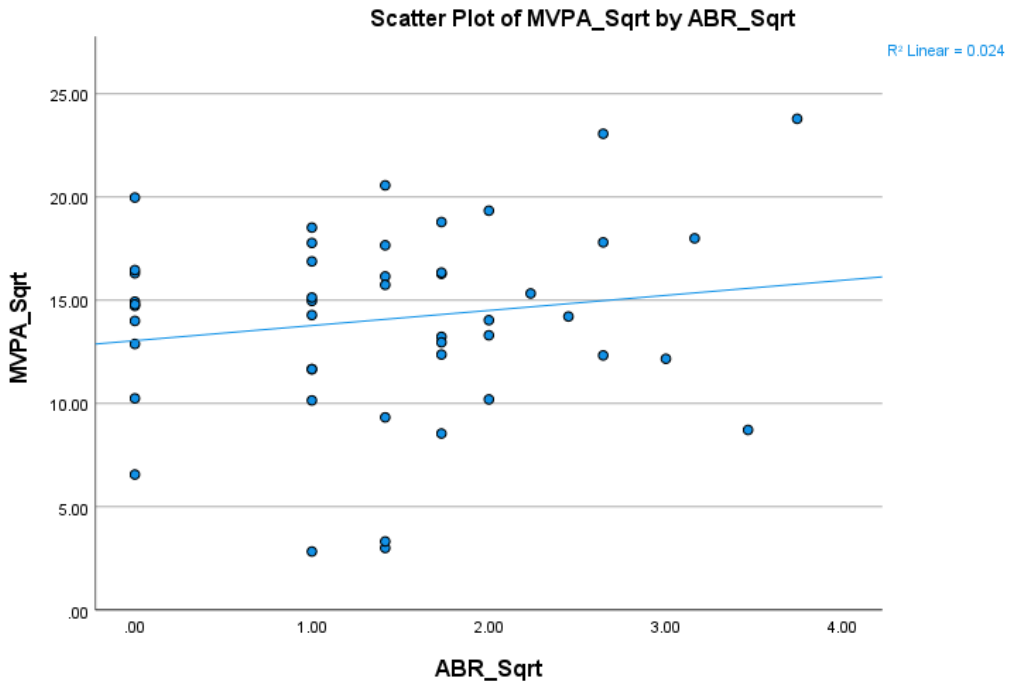


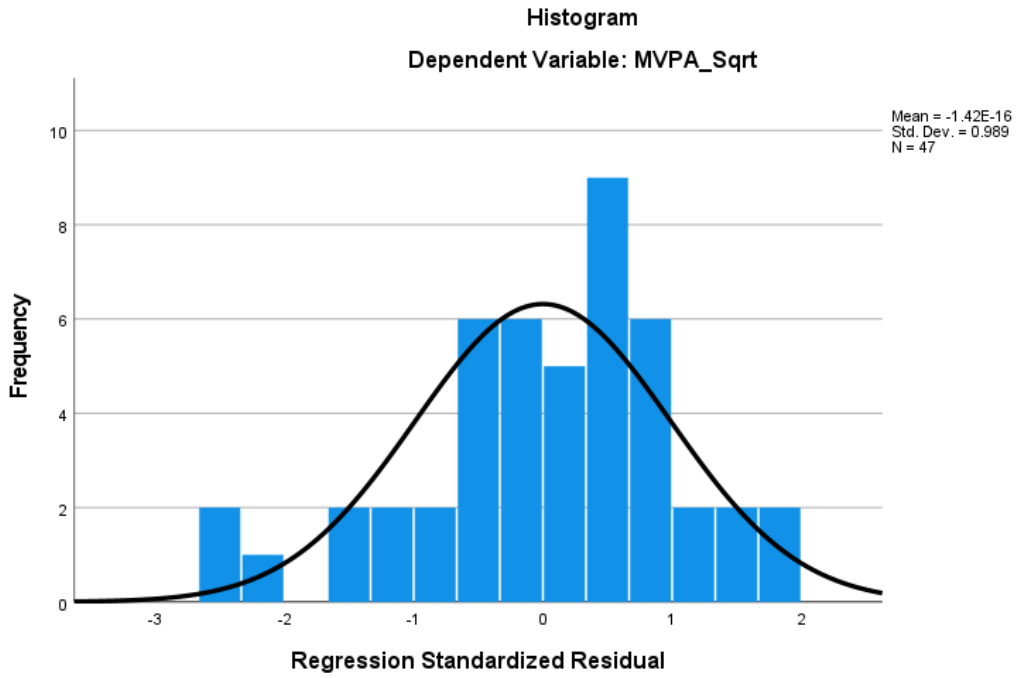


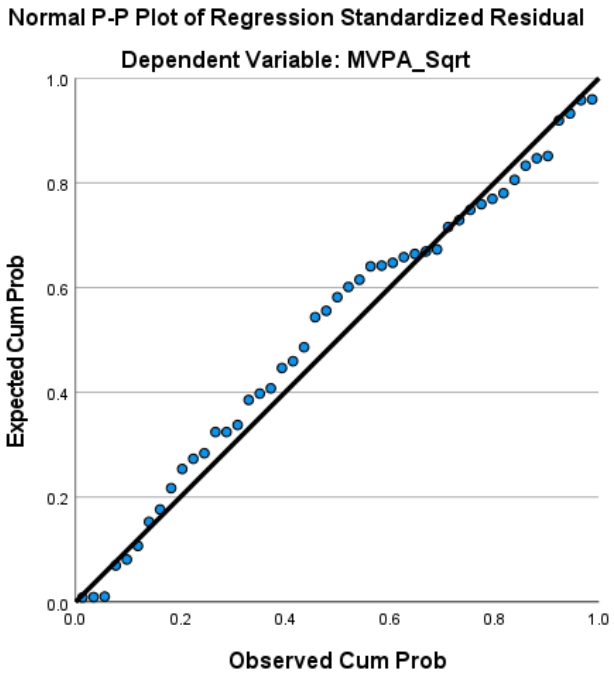

Normal P-P Plot of Regression Standardized Residual
Dependent Variable: MVPA mins
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0

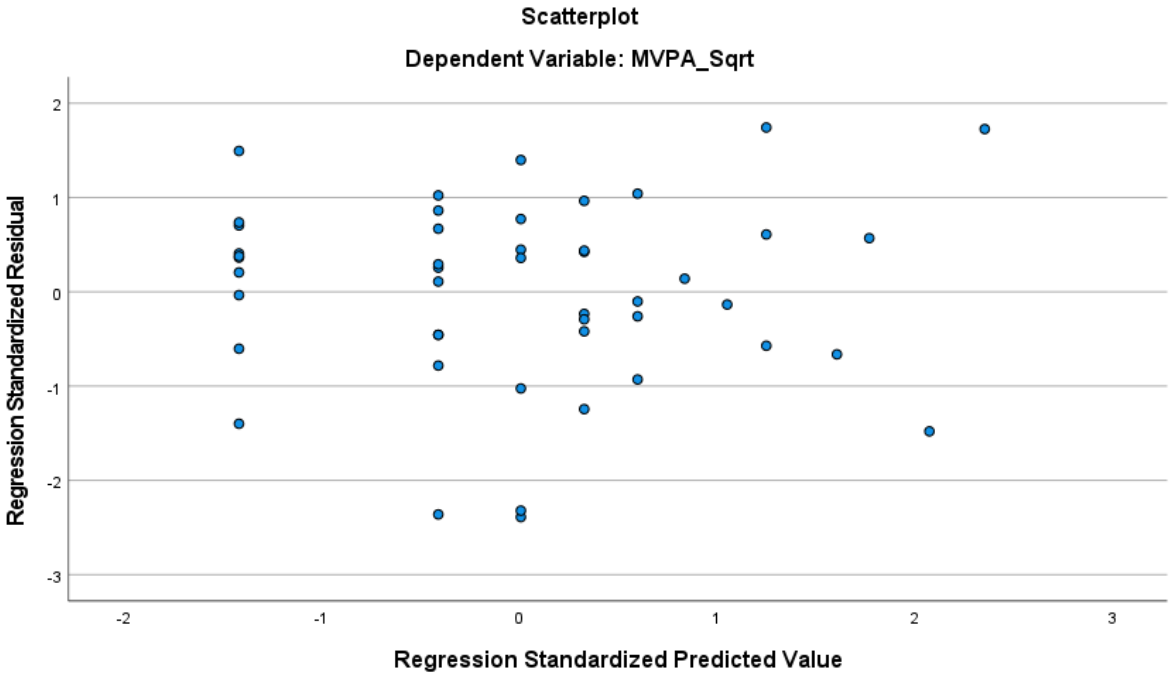

Scatterplot
Dependent Variable: MVPA mins
Regression Standardized Residual
Regression Standardized Predicted Value
4
3
2
1
0
-1
-2

Appendix XX: Residuals of Annualised Bleeding Rate (ABR) and Moderate-Vigorous Physical Activity (MVPA) (outlier removed, variables transformed) (Chapter 3)

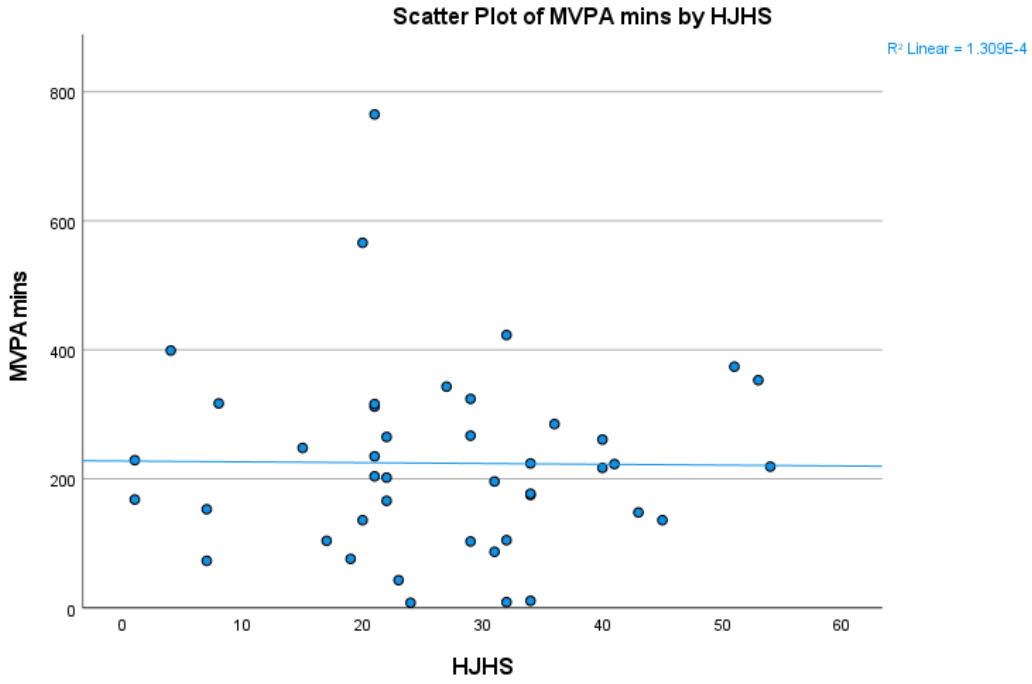


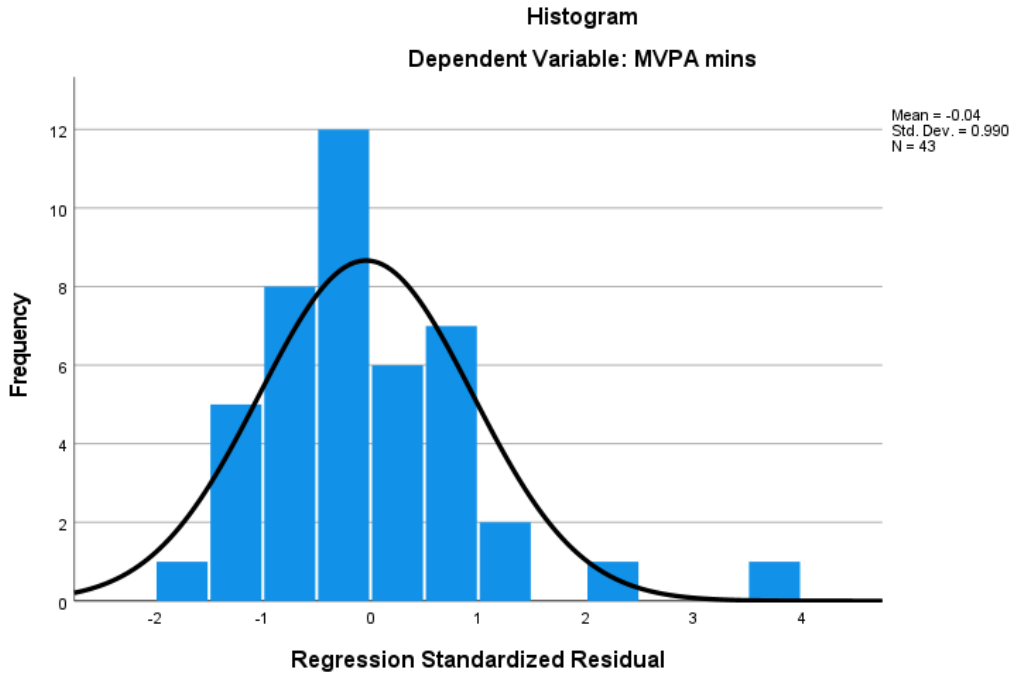


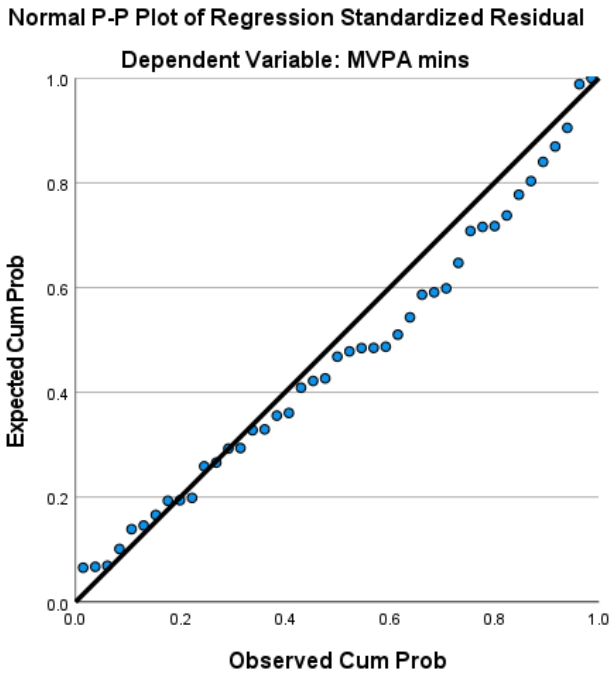

Normal P-P Plot of Regression Standardized Residual
Dependent Variable: MVPA_Sqrt
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0

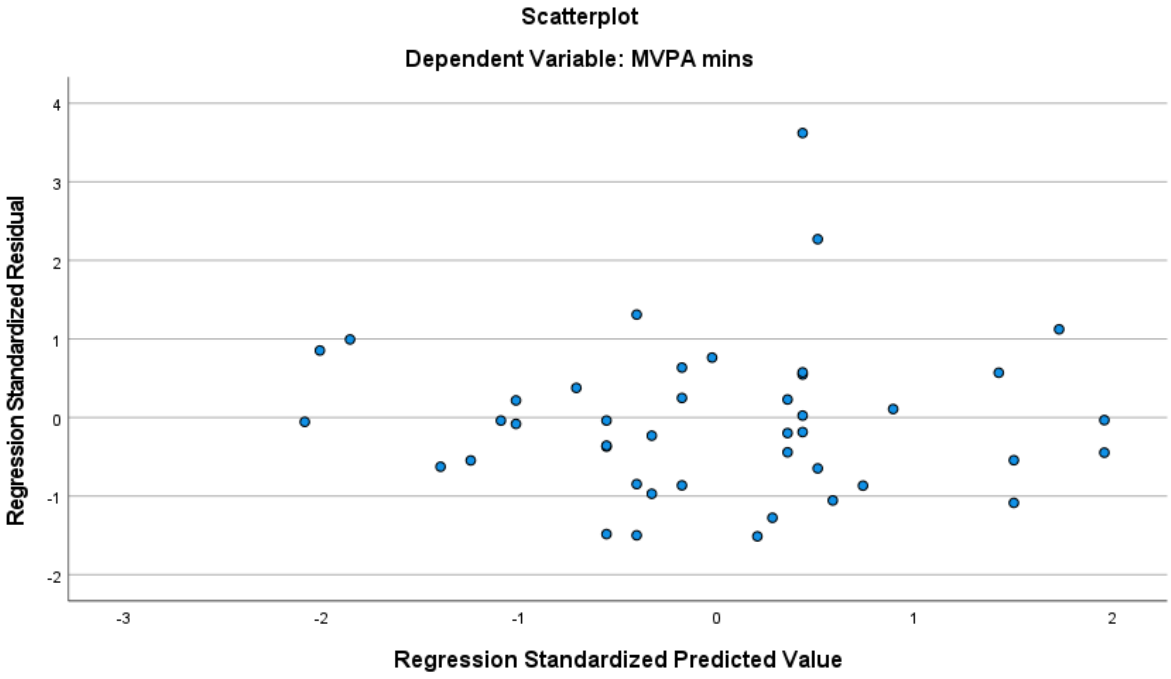

Scatterplot
Dependent Variable: MVPA_Sqrt
Regression Standardized Residual
Regression Standardized Predicted Value
2
1
0
-1
-2
-3
-2
-1
0
1
2
3

Appendix XXI: Residuals of the Haemophilia Joint Health Score (HJHS) and Moderate-Vigorous Physical Activity (MVPA) (outlier included) (Chapter 3)

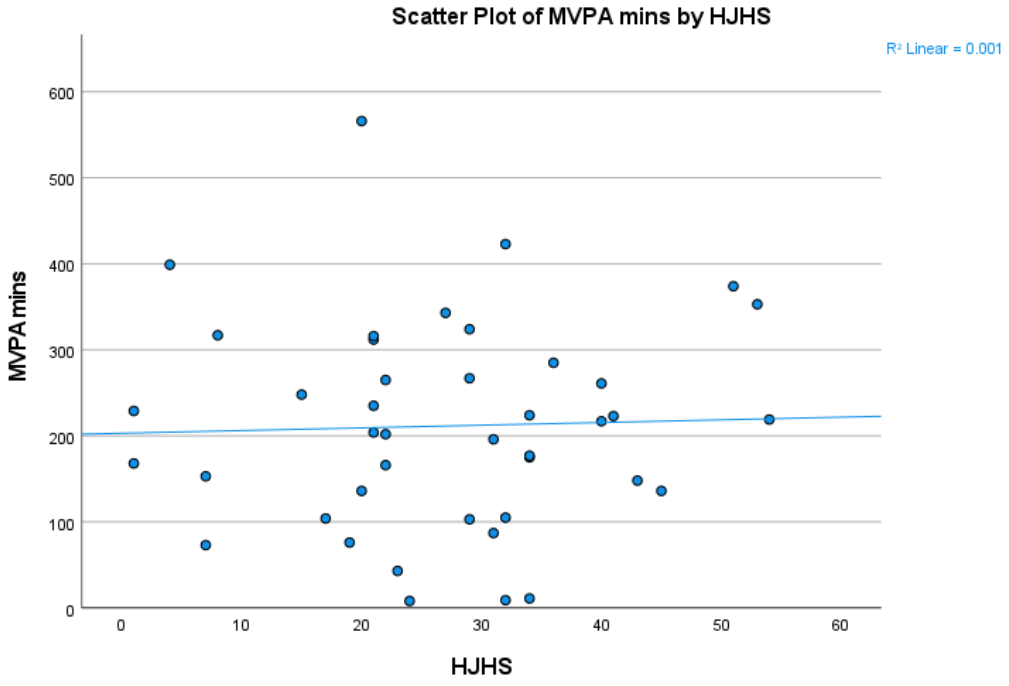


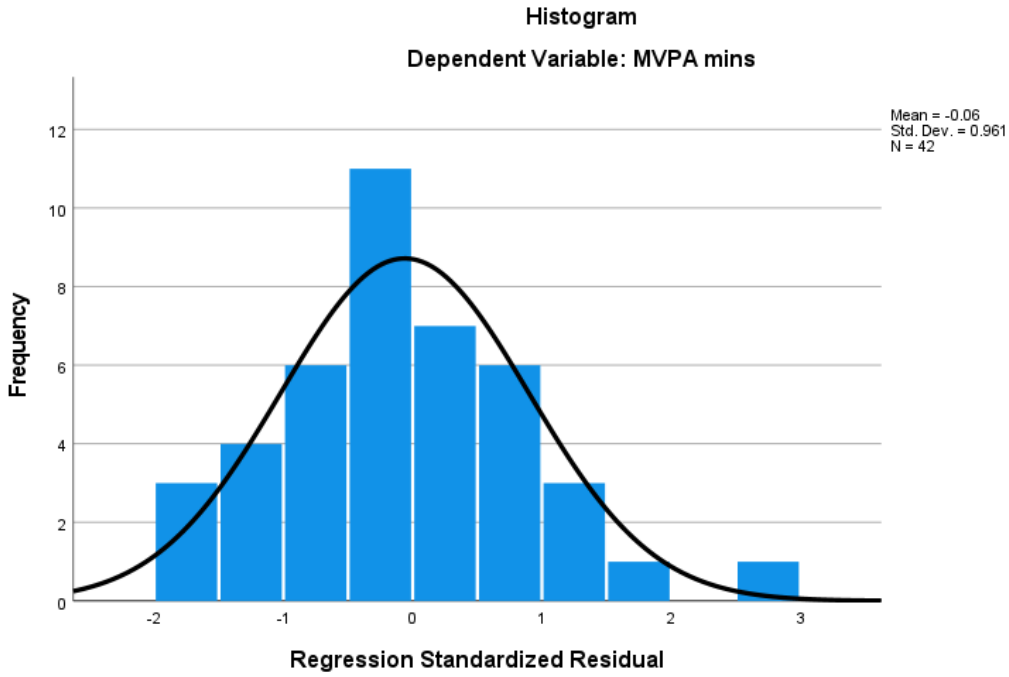


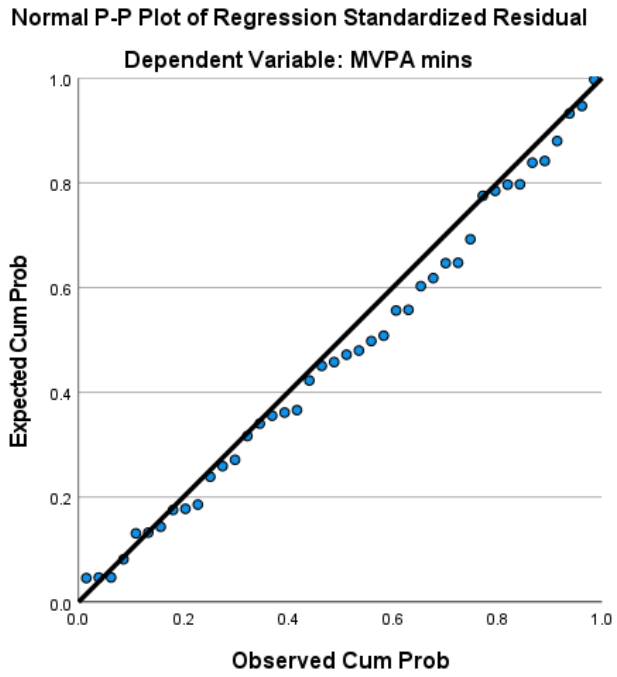

Normal P-P Plot of Regression Standardized Residual
Dependent Variable: MVPA mins
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0

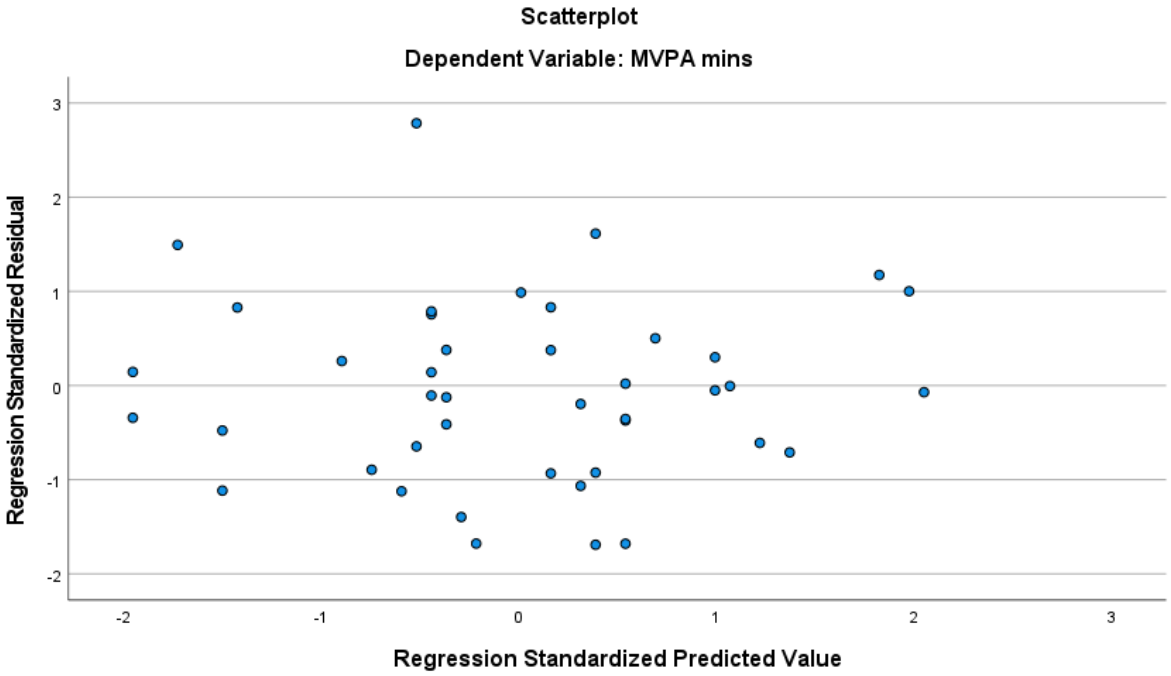

Scatterplot
Dependent Variable: MVPA mins
Regression Standardized Residual
Regression Standardized Predicted Value
4
3
2
1
0
-1
-2
-3
2

Appendix XXII: Residuals of Haemophilia Joint Health Score (HJHS) and Moderate-Vigorous Physical Activity (MVPA) (outlier removed) (Chapter 3)

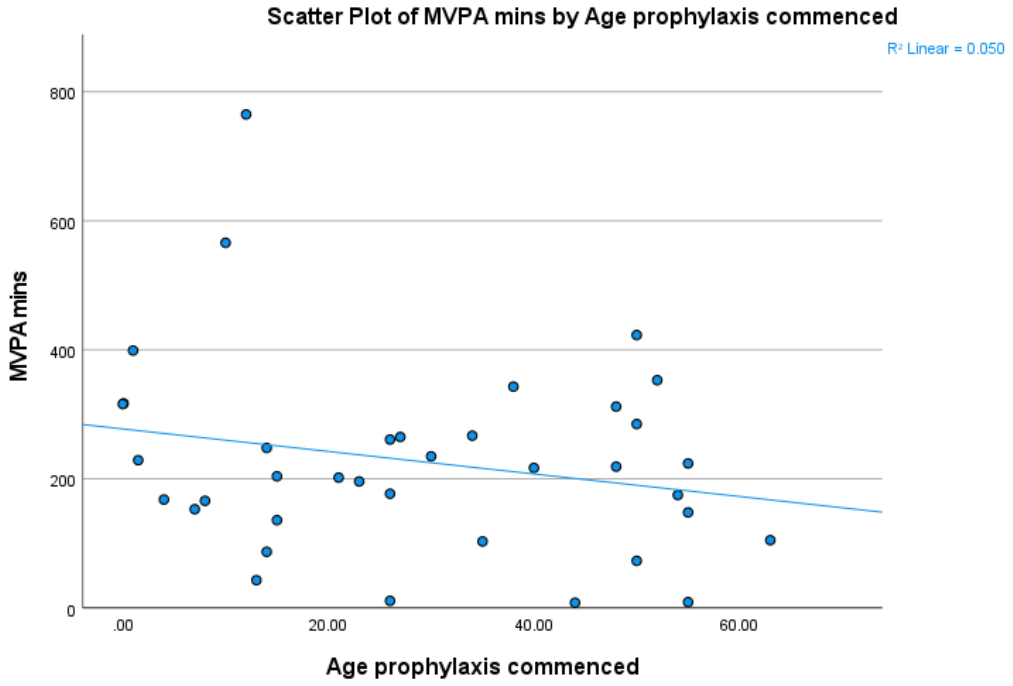


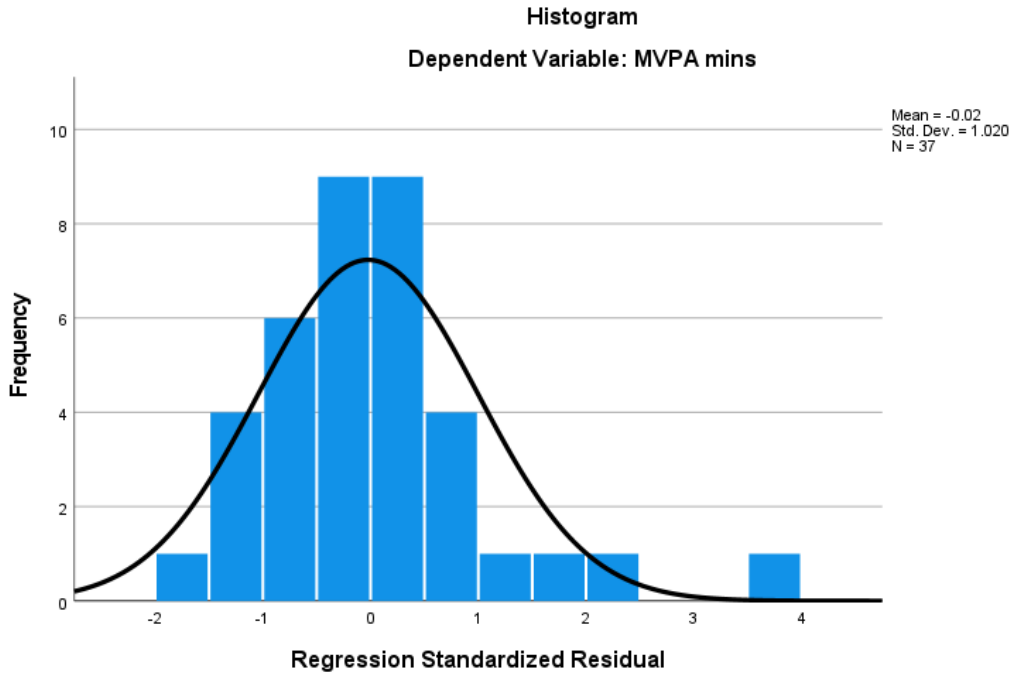


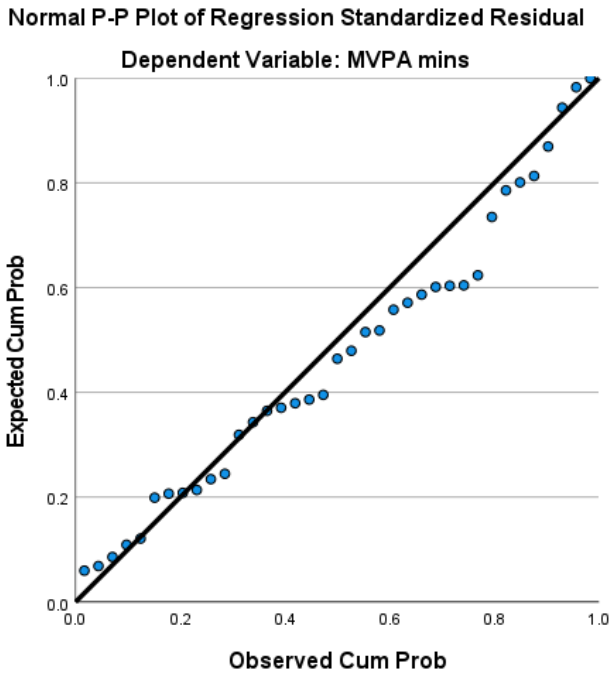

Normal P-P Plot of Regression Standardized Residual
Dependent Variable: MVPA mins
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0

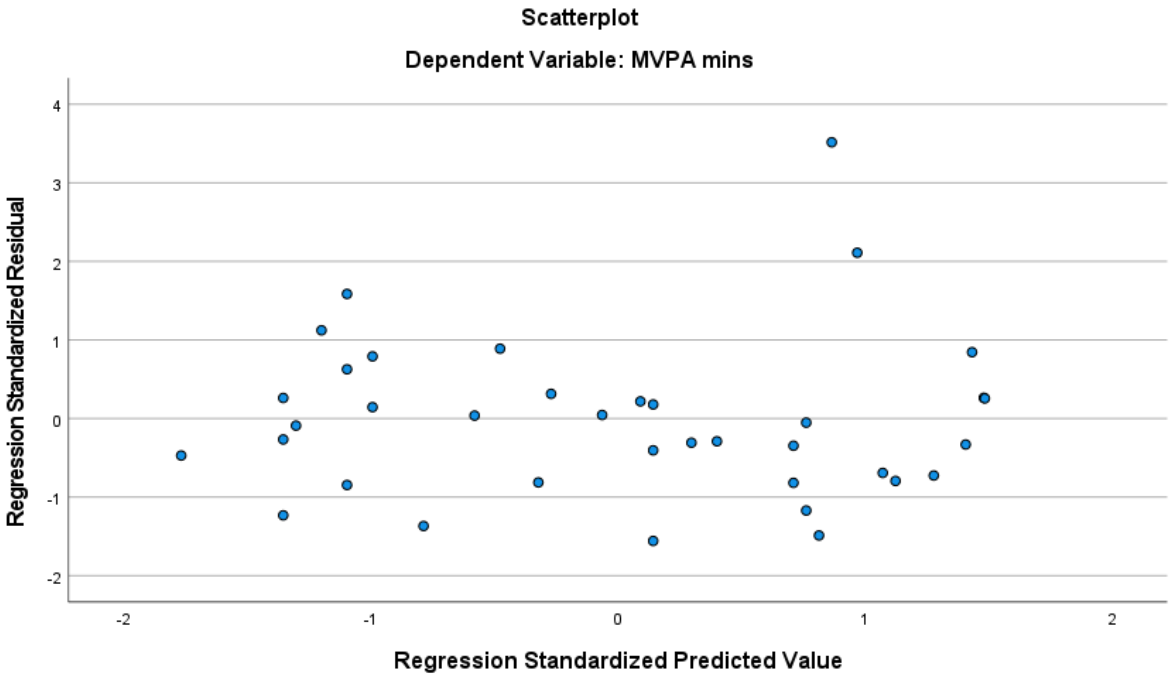

Scatterplot
Dependent Variable: MVPA mins
Regression Standardized Residual
Regression Standardized Predicted Value
3
2
1
0
-1
-2

Appendix XXIII: Residuals of age at which prophylaxis was commenced and Moderate-Vigorous Physical Activity (MVPA) (outlier included) (Chapter 3)

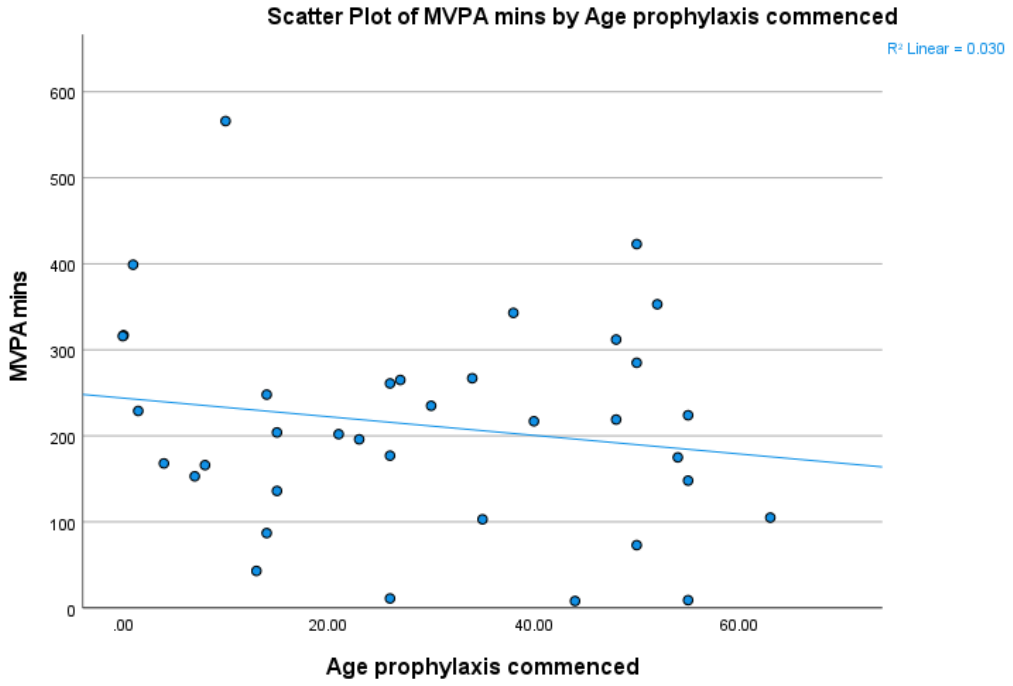


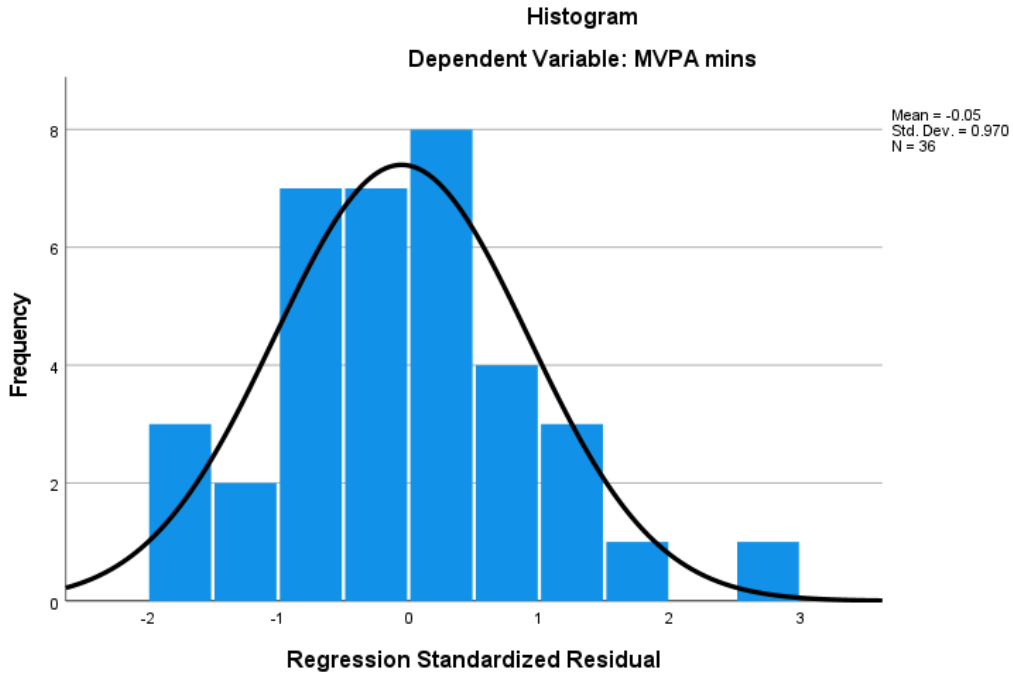


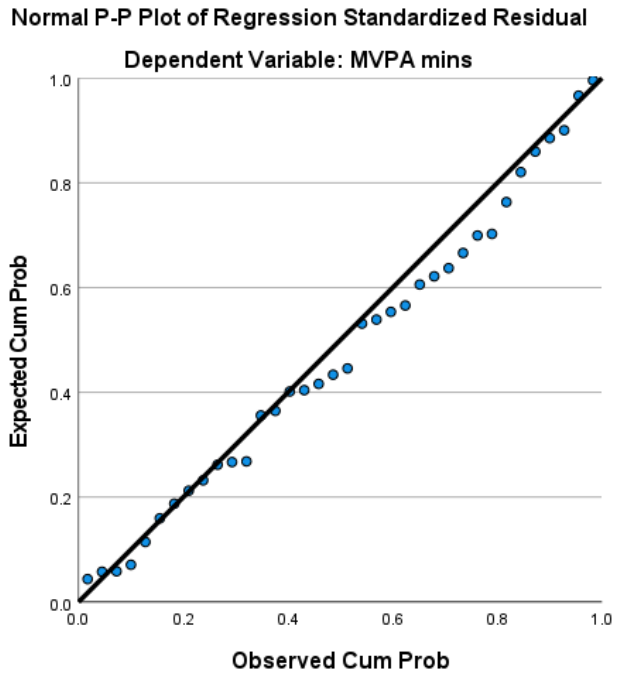

Normal P-P Plot of Regression Standardized Residual
Dependent Variable: MVPA mins
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0

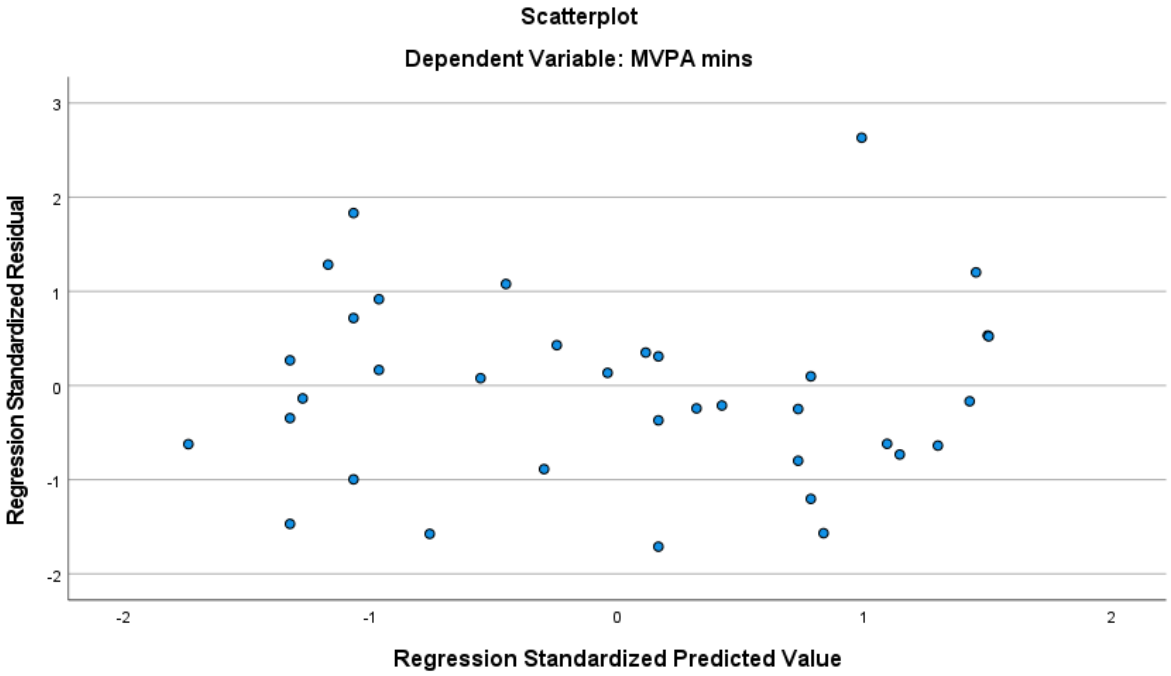

Scatterplot
Dependent Variable: MVPA mins
Regression Standardized Residual
Regression Standardized Predicted Value
4
3
2
1
0
-1
-2

Appendix XXIV: Residuals of age at which prophylaxis was commenced and Moderate-Vigorous Physical Activity (MVPA) (outlier removed) (Chapter 3)






Normal P-P Plot of Regression Standardized Residual
Dependent Variable: MVPA mins
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0


Scatterplot
Dependent Variable: MVPA mins
Regression Standardized Residual
Regression Standardized Predicted Value
3
2
1
0
-1
-2

Appendix XXV: Participant information leaflet for Study IV

Participant Information Leaflet

The Irish Personalized Approach to the Treatment of Haemophilia (iPATH) Study: A Follow-up of Physical Activity and Quality of Life in Adults with Haemophilia in Ireland from the iPATH Study

The Research Team:

Lead Investigator: Prof. John Gormley

Co-Investigators: Prof. James O' Donnell & Dr. Michelle Lavin

Research Physiotherapist: Ms. Megan Kennedy

INTRODUCTION: Before you decide whether or not you wish to take part in this study, you should read the information provided in this leaflet carefully. Ask questions – don't feel pressured to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is called 'Informed Consent'. You may wish to discuss it with your family, friends or medical team.

WHO IS CARRYING OUT THIS RESEARCH? Researchers from the School of Physiotherapy in Trinity College, Dublin are carrying out this study to investigate how healthy and active people with haemophilia in Ireland are. They are also investigating how health relates to bleeding tendencies between individuals.

PART 1 – THE STUDY

WHY THIS STUDY IS BEING DONE AND WHY HAVE YOU BEEN ASKED TO TAKE PART? It has been over two years since the first iPATH Physical Activity research assessments were carried out. During this time, new treatments for haemophilia have been invented and many people with haemophilia (PwH) may or may not have changed treatment. The iPATH team are interested to know whether physical activity habits and lifestyle have changed over the past two years for those who partook in the initial research assessment. Furthermore, the global Covid-19 pandemic has affected the lives of everyone during the past year. The team are also interested to know about the impact Covid-19 has had on the physical activity habits and lives of PwH.

AIM: The aim of this study is do a long-term follow-up of physical activity levels in adults with moderate and severe haemophilia from the iPATH study. Additionally, the impact of Covid-19 on physical activity and quality of life will be examined.

WHAT IS INVOLVED IF YOU AGREE TO PARTICIPATE: If you decide to take part in this part of the study, the ActiGraph physical activity monitor will be sent to your house. The monitor is the same one you would have worn whilst taking part in the first study (see the picture below). Prior to sending the monitor, the researcher will ask you your most recent height and weight in order to set up your activity monitor. **You will be asked to wear the monitor for 7 days in a row from the day after you receive it.** The monitor is about the size of a matchbox and records your movements while awake. It measures activity during the day such as walking running, cycling, doing housework, etc. The device is not to be worn in the shower/bath or while swimming as it is not water – resistant. You will be provided with an information leaflet about how to use and wear the monitor and an activity log sheet to record any activity you partook in when not wearing the accelerometer (e.g. swimming). We will arrange for the monitor to be collected from you and sent back to the researcher once you are finished with it. After you have completed the monitor you will be sent a questionnaire which will ask for more detail on your physical activity, as well as your quality of life and the impact the past year has had on your life.

MEDICAL RECORD ACCESS: With your consent to taking part in the first study you gave permission to the research team to access your medical records for analysis purposes related to this study. This will continue if you agree to take part in this part of the study. This includes information about your gender, age, clinical information about haemophilia, such as bleeds, treatment history, joint health scores and any other relevant past medical history because these are factors which may affect how physically active you are.

BENEFITS: An update on your physical activity levels will be provided upon completion of the assessment if you desire in the form of an individualised report, which may be of potential benefit

in informing your future healthcare and lifestyle choices. Participating in this study will also add to this field of research and inform the need for services related to health and physical activity.
RISKS: There are no physical risks associated with this study. If you do not feel well during the study period, please inform your medical team and do not continue with the study.
The inclusion and exclusion criteria for this part of the study are unchanged from the first part (please see the previous Participant Information Leaflet you received).

PART 2 – DATA PROTECTION

WHAT INFORMATION ABOUT YOU (PERSONAL DATA) WILL BE USED AS PART OF THIS STUDY AND WHY IS IT BEING USED? Personal data collected about you will include your gender, age, clinical information about haemophilia, bleeds, treatment history, joint health scores, bone mineral density and any other relevant past medical history will be gathered from the clinical database and medical records as these are factors which may affect how active you are. Information on your body composition, physical activity and quality of life will be collected. This information is needed to determine the aims of the study. Your physical activity levels will also be profiled (placed into a category) as to whether they are currently meeting recommended physical activity guidelines.
HOW WILL YOUR PERSONAL DATA BE PROTECTED? All of your information is assigned a study ID code by the research team (in a process called pseudonymisation). This coding process is linked to your personal data and is intended to mask your identity. **Personal identifiers, such as your name or date of birth, are never used to label your study information.** The codes linked to your personal information are secured in a locked cabinet and on a password protected database in the National Coagulation Centre. Your study results will be coded and stored on an electronic database in a secure password protected PC in a locked office and any paper forms will be stored in a locked cabinet in the Trinity Centre for Health Sciences, St. James's Hospital. Only personal data which is relevant for the purpose of the study is used (a concept called data minimisation). The ActiGraph monitor needs to be traced back to you so this information will be pseudonymised, however the questionnaire will be fully anonymised and will not contain any personally identifiable information and cannot be traced back to you.
WHO HAS ACCESS TO YOUR DATA AND HOW WILL YOUR DATA BE USED? Only the research team have access to your data and will be involved in analysing and processing it. The data processors include the study investigators and research physiotherapist. Your results will be grouped with other study results and analysed to establish your physical activity levels as well as its association with the other factors outlined in the aims section of this leaflet. The overall study findings will be published in international peer reviewed journals and be shared within presentations at national and international meetings. Your personal data will remain pseudonymised and your name and personal details will not be published or disclosed to anyone outside of this study.
WHO CONTROLS ACCESS TO YOUR DATA, HOW YOUR DATA WILL BE STORED AND HOW LONG WILL YOUR DATA BE STORED FOR: St. James's Hospital and Trinity College Dublin are the data controllers. All information relating to you will be stored and locked in a secure office in the NCC, only accessible by the research team. Your study results will be coded (pseudonymised) and stored on an electronic database in a secure password protected PC in a locked office in the Trinity Centre for Health Sciences. Any paper forms related to the study will be stored in your medical file and a copy will be stored in the research file (which will be securely stored and locked away in a locked cabinet in the NCC). Data will be stored for a total of 10 years to allow sufficient time for analysis and potential publications related to the research. It will then be destroyed appropriately by the research team.
IS THERE ANY RISK INVOLVED WITH PROCESSING AND STORING YOUR DATA AND WHAT WILL BE DONE IF THERE IS A BREACH: Considering sensitive personal data relating to your health and behaviour is involved, in the unlikely event of a data breach (i.e. data being mislaid, lost or stolen) you will be notified as soon as possible and it will be reported immediately to the Data Protection Commissioner.
WHAT IS THE LAWFUL BASIS TO USE YOUR PERSONAL DATA? Your data will be processed under the lawful basis of Article 6(1)(e) and 9(2)(j) of the EU General Data Protection Regulation Act 2016.
IF YOU WITHDRAW FROM THE STUDY WHAT WILL HAPPEN TO YOUR DATA: You may withdraw consent from the study if you so wish at any time and your data will not be included in the analysis, it will be securely destroyed by the study investigators.

For more information about your rights under the General Data Protection Regulations (GDPR) please visit : https://www.dataprotection.ie/en/individuals

PART 3 – COSTS, FUNDING

VOLUNTARY PARTICIPATION AND STUDY WITHDRAWAL: If you have volunteered to participate in this study, you may withdraw participation at any time. If you decide not to participate, or if you withdraw consent, you will not be penalized and will not give up any benefits which you had before entering the study. You should not feel in any way obliged to take part in this study. If you wish to seek more information about this study, please contact the research physiotherapist (Ms. Megan Kennedy) directly. You may withdraw consent from the study if you so wish at any time and your data will not be included in the analysis.

COMPENSATION: The research team covered by standard clinical indemnity. Nothing in this document restricts or curtails your rights.

STOPPING THE STUDY: You understand that the research team may stop your participation in the study at any time without your consent.

WILL IT COST YOU TO TAKE PART? There are no financial costs involved with partaking in this study.

HAS THIS STUDY BEEN APPROVED BY A RESEARCH ETHICS COMMITTEE? WHO IS FUNDING THE STUDY? WILL RESULTS BE USED FOR COMMERCIAL PURPOSES? This research project has ethical approval Tallaght/ St. James's Research Ethics Committee approval received on 10th November 2017. This study is funded in part by a SFI Strategic Partnership Programme research grant from Science Foundation (SFI) and research support from Baxalta US Inc., a Takeda company. Study results will not be used for commercial purposes.

PART 4 – FURTHER INFORMATION

For more information or answers to your questions about the study, your participation in the study and your rights or if you wish to make a complaint, please see the contact details below:

Research Physiotherapist and Data Processor: Ms. Megan Kennedy, Discipline of Physiotherapy, Trinity Centre for Health Sciences, St James's Hospital. Contact Details: Tel (01) 8963613; Email: kennedme@tcd.ie

Lead investigator: Prof. John Gormley. Contact Details: Tel (01) 8962121; Email: jgormley@tcd.ie

Data Protection Officer: Data Protection Trinity College Dublin. Contact Details: dataprotection@tcd.ie

Will I be contacted again? You may be contacted again by the researchers in relation to your study results if you express that would like to receive feedback on them. With your explicit consent, you may also be contacted again by the researchers in relation to the current as well as other research studies of this nature.