‘A Profile of Physical Performance Variables in an Out-Patient Adult Population with Narcolepsy’

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Summary

Narcolepsy is a chronic, lifelong, disabling condition that affects an individuals' ability to regulate sleep-wake patterns. Narcolepsy is a condition that can significantly affect an individual's overall functioning by imparting a deleterious effect on their social wellbeing, physical wellbeing and employment (Schiappa et al., 2018). Quality of life in people with narcolepsy is significantly lower than the general population, with physical role limitations and vitality commonly being the most affected quality of life domains (Becker et al., 2004, Campbell et al., 2011, Dodel et al., 2007, Vignatelli et al., 2004). Despite this, the overall physical performance of this population remains relatively unknown.

The purpose of this thesis was to explore physical performance in people with narcolepsy. A systematic review and meta-analysis was initially conducted to explore health-related quality of life in people with narcolepsy which provided a subjective insight into how people with narcolepsy perceived their quality of life and physical wellbeing. A profiling study was then undertaken which attempted to comprehensively assess the physical performance of adults with narcolepsy attending the Narcolepsy Clinic in St. James's Hospital as an outpatient. Furthermore, this study aimed to explore: i) how symptom severity and quality of life interact with physical performance and ii) explore the feasibility of conducting research relating to physical performance in this population and the selected measures included in the test battery. Due to the heterogeneity of this sample, broad and inclusive outcome measures were selected with age-and-gender matched normative values to enable comparison. Ethical approval for this study was obtained from the St. James's Hospital and Tallaght University Hospital Research Ethics Committee.

The physical performance test battery included the following measure; cardiopulmonary fitness (YMCA Submaximal Bike Test), muscle strength (Dynamometry and Countermovement Jump Test), muscle endurance (American College of Sports Medicine Push Up Test and Wall Squat Test) and physical activity (Actigraphy). A number of questionnaires were utilised to assess health-related quality of life (Short Form 36 and Functional Outcomes of Sleep Questionnaire), symptom severity (Narcolepsy Severity Scale and Epworth Sleepiness Scale) and physical activity (Physical Activity Vital Sign and Sedentary Behaviour Questionnaire) of this sample. Several open-ended questions were asked to ascertain participants' attitudes towards exercise and their physical performance.

A total of 23 participants were recruited in this study. The majority of participants were female (n=13, 56.52%). The mean age (± SD) was 31.53 (± 13.17) years with a range of 20-63 years. Participants were concentrated in the 20-29 year age group (n=14, 60.87%). With the exception of Actigraphy, there was a high adherence level to the test battery. Physical performance was generally found to be lower than age-and-gender matched normative values for cardiopulmonary performance, physical activity and muscle strength and endurance. Symptom severity was high as measured by the Narcolepsy Severity Scale and Epworth Sleepiness Scale, and participants reported reduced quality of life when compared to general population norms. Furthermore, an interrelationship was identified between participants' physical performance, health-related quality of life and symptom severity. Analysis of the open-ended questions provided valuable insights into the difficulties experienced with exercising in people with narcolepsy.

In summary, this study profiled the physical performance of a sample of people with narcolepsy attending the Narcolepsy Clinic in St. James's Hospital as an outpatient. This study also trialled the physical test battery employed in this study, and the feasibility of conducting research in this population. In this sample of people with narcolepsy, physical performance was found to be markedly reduced than normative values, irrespective of participant age, gender and BMI. The chosen test battery employed in this study was largely feasible, and participants were enthusiastic and receptive towards the study. The interrelationship identified between physical performance, symptom severity and quality of life warrants further exploration of the role of physical activity and exercise in improving the physical performance in people with narcolepsy, and the influence of exercise on health-related quality of life and symptom severity in this cohort.

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Abstract

Background: Narcolepsy is a disabling lifelong condition that impacts an individuals' ability to regulate sleep-wake patterns. Narcolepsy can significantly impact the physical and mental wellbeing of people with narcolepsy, and has been associated with significant reductions in quality of life and physical performance. Despite physical functioning and vitality being the most affected domains of health-related quality of life in this cohort, more accurate measurements of physical performance using a suitable physical test battery have not yet been conducted.

Methods: A systematic review and meta-analysis was conducted to explore health-related quality of life in adults with narcolepsy. A cross-sectional study was conducted to assess the physical performance of adults with narcolepsy who attended the Narcolepsy Clinic in St. James's Hospital between October 2019 and March 2020. A comprehensive battery was designed to assess physical performance variables. The following variables were objectively assessed; cardiopulmonary fitness (YMCA Submaximal Bike Test), muscle strength (Dynamometry and Countermovement Jump Test), muscle endurance (ACSM Push Up Test and Wall Squat Test) and physical activity (Actigraphy). A number of questionnaires were utilised to assess health-related quality of life (Short Form 36 and Functional Outcomes of Sleep Questionnaire), symptom severity (Narcolepsy Severity Scale and Epworth Sleepiness Scale) and physical activity (Physical Activity Vital Sign) and sedentary behaviour (Sedentary Behaviour Questionnaire) of this sample. Several open-ended questions were asked to ascertain participants' attitudes towards exercise and their physical performance.

Results: In total, 23 participants completed the test battery. The majority of participants were female (n=13, 56.52%). The mean age (± SD) was 31.53 (13.17) years with a range of 20-63 years observed. The majority of participants were concentrated in the 20-29 age group (n=14, 60.87%). Physical performance was generally found to be lower than age-and-gender matched normative values for cardiopulmonary fitness, physical activity and muscle strength and endurance. Symptom severity was high as measured by the Narcolepsy Severity Scale and Epworth Sleepiness Scale, and participants reported significantly reduced quality of life when compared to general population norms. Analysis of the open-ended questions provided valuable insights into the difficulties experienced with exercising in people with narcolepsy. Furthermore, an interrelationship was identified between participants' physical performance, health-related quality of life and symptom severity.

Conclusion: In this sample of people with narcolepsy, physical performance was found to be markedly reduced than normative values, irrespective of participant age, gender and BMI. The chosen test battery employed in this study was largely feasible, and participants were enthusiastic and receptive towards the study. The interrelationship identified between physical performance, symptom severity and quality of life warrants further exploration of the role of physical activity and exercise in improving the physical performance in people with narcolepsy, and the influence of exercise on health-related quality of life and symptom severity in this cohort.

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List of Abbreviations

AASM	American Academy of Sleep Medicine
ACSM	American College of Sleep Medicine
BMI	Body Mass Index
DNS	Disrupted Night-time Sleep
EDS	Excessive Daytime Sleepiness
EQ5D	EuroQol-5D
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
GDPR	General Data Protection Regulation
HRQoL	Health-Related Quality of Life
JBI	Joanna Briggs Institute
MCS	Mental Component Summary
MVPA	Moderate-Vigorous Physical Activity
NC	Narcolepsy with Cataplexy
NINDS	National Institute of Neurological Disorders and Stroke
NSS	Narcolepsy Severity Scale
NT1	Type 1 Narcolepsy – Narcolepsy with Cataplexy
NT2	Type 2 Narcolepsy – Narcolepsy without Cataplexy
NWC	Narcolepsy without Cataplexy
PAVS	Physical Activity Vital Sign
PCS	Physical Component Summary
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Registry of Systematic Reviews
SEDBQ	Sedentary Behaviour Questionnaire
SF8	Short Form 8
SF12	Short Form 12
SF36	Short Form 36
VAS	Visual Analogue Scale
WHO-5	World Health Organisation – Five Wellbeing Index
WHOBREF	World Health Organization Quality of Life – BREF
YMCA	Young Men’s Christian Association

Chapter 1: Introduction

1.0 Introduction

1.1 Overview

The term “Narcolepsy” derives from the Greek words “narco” and “lepsy” which translates into a fit of stiffness. Narcolepsy is a disabling neurological condition that affects an individual’s ability to regulate sleep-wake patterns. This chronic sleep disorder is characterised by excessive daytime sleepiness and is frequently associated with episodic muscular weakness, known as cataplexy, following intense emotions such as laughter or anger. The presence of cataplexy is thought to be pathognomonic and is used to distinguish narcolepsy with cataplexy (type 1 narcolepsy) from narcolepsy without cataplexy (type 2 narcolepsy). Disrupted night-time sleep (DNS) is frequently reported by people with narcolepsy and may be associated with sleep paralysis and hallucinations (Roth et al., 2013). Narcolepsy is thought to have an incidence of 25-50 per 100,000 people, or 0.74 per 100,000 person-years (Longstreth et al., 2007). Additionally, a slight male predominance has been identified in males with incidence rates (1.6:1) and prevalence (1.8:1) in narcolepsy (Silber et al., 2002). Ireland experienced an increased number of cases of narcolepsy following the 2009-2010 Swine Flu epidemic with crude associations identified in pandemic-vaccination recipients (O’Flanagan et al., 2014). This increase of cases was also observed in other European countries such as Norway (Heier et al., 2013), Finland (Nohynek et al., 2012, Partinen et al., 2012), and Sweden (Szakacs et al., 2013).

1.2 Characteristics

Excessive daytime sleepiness (EDS) is present in both type 1 and type 2 narcolepsy, making it the most common symptom reported by people with narcolepsy (Wozniak and Quinnell, 2015). EDS presents as an increased likelihood of falling asleep in relaxing or sedentary situations, or a requirement for the exertion of additional effort to avoid falling asleep in the aforementioned situations (Nishino and Mignot, 1997). People with narcolepsy generally feel refreshed after brief naps; however, their sleepiness quickly returns within several hours, particularly when sedentary (Scammell, 2015). People with narcolepsy may also experience “sleep attacks” which manifest as unavoidable or overpowering urges to fall asleep (Goswami et al., 2016). People with narcolepsy generally maintain normal levels of alertness in the interim period between sleep attacks, especially if engaging in activities that hold their attention (NINDS, 2020). These sleep attacks are not immediate lapses into sleep but are instead representative of extreme sleepiness in those with significant sleep deprivation that can be observed in narcolepsy or other severe sleep disorders (Goswami et al., 2016). The clinical presentation of EDS is broad, and its’ manifestation can vary through related symptoms such as fatigue, reduced energy levels, lethargy, apathy, irritability, and automatic behaviours (Bogan, 2007).

Cataplexy

The presence of cataplexy in type 1 narcolepsy is due to a hypocretin deficiency caused by the destruction of most of the hypocretin-producing neurons located in the hypothalamus (Liblau et al., 2015). Cataplexy is most commonly triggered by positive emotions such as laughter, hearing jokes, feelings of excitement, or elation (Krahn et al., 2005). A visualisation of the cataplectic spectrum can be seen below in Figure 1. Partial cataplexy attacks often begin in the facial musculature, presenting as jaw slackening or a short dropping of the head. General cataplexy can be more pronounced, particularly if the trunk or limbs are affected. Such episodes can result in individuals falling to the ground (Golden and Lipford, 2018). People who experience an episode of cataplexy generally remain both alert and oriented to their surroundings during the attack, but may be unable to respond (Goswami et al., 2016). Cataplectic episodes generally last several minutes, but very rarely episodes will last several hours, typically following cessation and withdrawal from antidepressant medications (Poryazova et al., 2005, Dauvilliers et al., 2014). The onset of cataplexy usually occurs near EDS onset, however, in approximately 10% of narcolepsy cases, cataplexy is the first symptom observed and can result in individuals with narcolepsy being misdiagnosed with seizure disorders (Scammell, 2015).

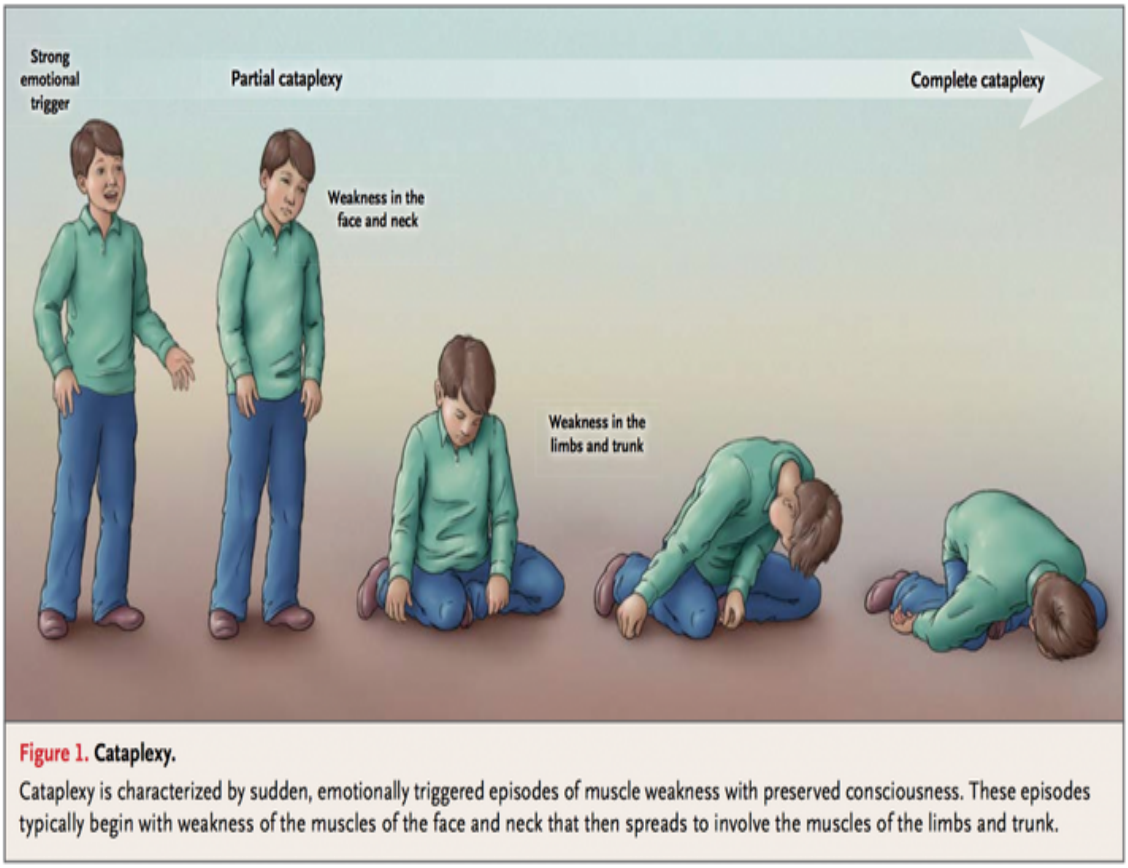


Figure 1. **Cataplexy.**
Cataplexy is characterized by sudden, emotionally triggered episodes of muscle weakness with preserved consciousness. These episodes typically begin with weakness of the muscles of the face and neck that then spreads to involve the muscles of the limbs and trunk.

Figure 1: Visualisation of the Spectrum of Cataplectic Episodes
Source: Figure from Scammell (2015)

Sleep paralysis is a common complaint in people with narcolepsy and is thought to arise from an intrusion of REM-induced muscle paralysis into wakefulness (Mahowald and Schenck, 2005). This phenomenon occurs in 3-5% of the general population, but has a much higher incidence in people with narcolepsy, affecting approximately 50-60% of this cohort (Nishino, 2007). Episodes of sleep paralysis generally occur when people are falling asleep or waking up. Individuals find themselves fully aware of their condition but unable to move, speak, or take deep breaths (Goswami et al., 2016). These episodes are transient and do not result in permanent dysfunction, with individuals readily recovering their ability to speak and move (NINDS, 2020). However, these episodes can be quite frightening, with approximately 90% of episodes associated with fear (Cheyne et al., 1999). Sleep paralysis has also been reported to be associated with fears of feeling suffocated, particularly with those inexperienced with sleep paralysis (American Academy of Sleep Medicine, 2005). This feeling of suffocation may be due to the inactivity of the accessory muscles of respiration; however, diaphragmatic activity ensures that adequate air exchange is maintained during sleep paralysis (Goswami et al., 2016).

Hallucinations are another common complaint in people with narcolepsy. Hallucinations can be hypnopompic or hypnagogic, depending on whether they occur upon awakening or prior to falling asleep, respectively, with the former occurring much more frequently (Golden and Lipford, 2018). Similar to sleep paralysis and cataplexy, hallucinations generally last for a few minutes. Hallucinations experienced in narcolepsy can be distinguished from those experienced by psychotic disorders as people with narcolepsy rarely experience complex auditory hallucinations or fixed delusions (Scammell, 2015). Instead, hallucinations in this population are often visual and vivid (Golden and Lipford, 2018). As hypnagogic hallucinations are relatively common in the general population, occurring in approximately one-fifth of people, the presence of hallucinations is much less helpful for diagnosing narcolepsy (Scammell, 2015). Furthermore, the presence of hallucinations can result in misdiagnosis, as the hallucinations commonly experienced during sleep paralysis can be mistaken for psychiatric symptoms (Waters et al., 2016).

Disrupted night-time sleep (DNS) has been reported to be a common complaint and frequent finding on polysomnographic testing in people with narcolepsy (Roth et al., 2013). Despite experiencing severe sleepiness, people with narcolepsy struggle to stay asleep and their sleep is extremely fragmented, resulting in several awakenings throughout the night (Golden and Lipford, 2018). This fragmented sleep may be caused by additional symptoms of narcolepsy such as insomnia, vivid dreaming, sleep apnoea, or periodic leg movements and can contribute to DNS (NINDS, 2020). DNS has been reported to be more of an issue than sleep paralysis and hallucinations by people with narcolepsy, with DNS having an estimated prevalence ranging from 30-95% (Roth et al., 2013).

1.3 Burden of Narcolepsy

Narcolepsy is a condition that can significantly affect an individual's overall functioning by imparting deleterious effects on their social and physical wellbeing (Schiappa et al., 2018). The significant symptom burden associated with narcolepsy can manifest in a multitude of ways, from impairment of mental health, social exclusion, increased healthcare usage, or impairment of employment and education (Kapella et al., 2015).

Psychiatric comorbidities are reportedly common in people with narcolepsy, with over half (57%) of this cohort reportedly exhibiting symptoms of depression (Daniels et al., 2001, Dauvilliers et al., 2009). In a study by Chellappa and Araújo (2006), excessive daytime sleepiness was shown to be significantly associated with higher levels of depression and suicidal ideation. This correlation supports the theory proposed by Morse and Sanjeev (2018) that the significant symptom overlap shared by narcolepsy and psychiatric illnesses contribute to the development of psychiatric comorbidities in people with narcolepsy. The significant symptom burden associated with narcolepsy has a major impact on the physical and psychosocial wellbeing of this cohort, and health-related quality of life (HRQoL) is often impaired as a consequence of this burden (Dodel et al., 2004). This reduced quality of life, particularly in younger adults with narcolepsy, has been associated with depression, occupational and academic difficulties, and deleterious effects on personal and social relations (Kapella et al., 2015).

People with narcolepsy experience a significant symptom and financial burden as a result of their condition. This burden may be attributed to the large direct and indirect costs associated with the condition, early symptom onset, decline in functioning, lack of a cure, and the need for lifelong treatment (Thorpy and Hiller, 2017). Compared to the general population, people with narcolepsy experience approximately twofold higher inpatient admissions, emergency department visits, outpatient visits, physician visits, and a 1.5-fold increase in excess mortality (Black et al., 2014, Ohayon et al., 2014). Increased healthcare utilisation is accompanied by increased annual direct medical costs, which are approximately twofold higher in people with narcolepsy than in matched-controls ($11,702 vs $5261, respectively; $P < .0001$)(Thorpy and Hiller, 2017). This financial burden perpetuates across all aspects of healthcare utilisation, with medications costing more than three times higher and hospitalisations costing three-to-four times higher in people with narcolepsy compared to the general population (Jennum et al., 2009). With sleep attacks being significantly correlated with higher indirect costs in people with narcolepsy than those without these attacks(Black et al., 2014), mitigating the significant symptom burden of this condition may reduce the socioeconomic impact in people with narcolepsy.

Narcolepsy has also been shown to impart a deleterious effect on employment and education, and occupational problems have long been recognised as a major psychosocial consequence of narcolepsy (Broughton et al., 1981, Daniels et al., 2001, Teixeira et al., 2004). In a study by Teixeira et al. (2004), 67% of respondents reported falling asleep in a workplace setting, and 52% of participants reported that they had left a job because of narcolepsy. Furthermore, a study by Dodel et al. (2004) identified that 59% of people with narcolepsy reported that they were unemployed, with 43% naming their narcolepsy as the reason for unemployment. Work-related productivity is also affected in people with narcolepsy, with higher costs relating to absenteeism ($7631 vs $12,839, P<0.001) and presenteeism ($4987 vs $7013; P <.001) observed when compared to matched controls (Flores et al., 2016). Even when employed, it was found that people with narcolepsy earn only two-thirds of controls' income in a study conducted by Jennum et al. (2009). Furthermore, narcolepsy has also been shown to increase workplace accidents (Broughton and Broughton, 1994), and early retirement (Dodel et al., 2004). This negative impact may be attributed to the age of diagnosis, as those diagnosed with narcolepsy have been shown to perceive their health as better, attain higher levels of education, and fewer problems with employment than those diagnosed later in life (Ingravallo et al., 2012).

1.4 Aims and Objectives of Thesis

The overall aims of this thesis were to:

i. Systematically review the literature appraising HRQoL in people with narcolepsy.
ii. Profile the physical performance of people with type 1 or type 2 narcolepsy that attend the Narcolepsy Clinic in St. James's Hospital as an outpatient.

The objectives of this thesis were as follows:

i. To provide pooled mean scores of the domains of the various HRQoL tools used in this population
ii. To compare HRQoL in people with narcolepsy to the general population and other chronic health conditions
iii. To explore the heterogeneity of the published studies, the tools used to assess HRQoL in this population and the influence of study characteristics on HRQoL.
iv. To profile the following variables: cardiopulmonary fitness, muscle strength, muscle endurance, physical activity, and sedentary behaviour in people with narcolepsy attending the Narcolepsy Clinic in St. James's Hospital.
v. To determine the quality of life and symptom severity of the study population.
vi. To compare the study populations' physical performance to general population norms.

vii. To compare the study populations’ quality of life to general population norms and other chronic health conditions.

viii. To explore the relationship between physical performance, quality of life, and symptom severity in the study population.

ix. To ascertain the study populations’ priorities and concern regarding their physical health, their barriers towards physical activity, and their perception of physiotherapy.

Chapter 2: Health-Related Quality of Life in Narcolepsy: A Systematic Review and Meta-Analysis

2.1 Systematic Review Introduction

Narcolepsy is a rare, disabling chronic neurological disorder that is characterised by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations and sleep paralysis. Narcolepsy can be divided into two main types: narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2), both of which have similar clinical presentations. However, NT1 is distinguished by the presence of cataplexy which is an episodic loss of muscle tone in full consciousness that generally occurs following intense emotions such as laughter or anger and decreased cerebrospinal fluid levels of hypocretin (Medicine, 2014). The incidence of narcolepsy is estimated to be 25-50 per 100,000 in western populations (Overeem et al., 2008). Symptom onset typically occurs in adolescence; however, approximately one-third of people with narcolepsy experience initial symptoms in adulthood (Dauvilliers et al., 2001).

Health-related quality of life (HRQoL) can be described as a “multidimensional concept that includes subjective reports of symptoms, side effects, functioning in multiple life domains, and general perceptions of life satisfaction and quality” (Revicki et al., 2014). Narcolepsy is a disabling neurological condition that carries a high risk for the development of social and occupational dysfunction (Morse and Sanjeev, 2018). This condition has been associated with considerable detriment to daily life including quality of life, occupational and academic difficulties and adverse effects on social and personal relationships (Emsellem et al., 2020, Flores et al., 2016, Kapella et al., 2015). With significant correlations identified between symptom severity and HRQoL (Dauvilliers et al., 2017), mitigating the deleterious effect of narcolepsy on HRQoL should be a critical therapeutic goal for people with narcolepsy.

The significant symptom burden and stigma associated with narcolepsy can negatively affect an individual’s quality of life and can contribute to depression, academic and employment difficulties, and personal and social issues, particularly in young adults (Kapella et al., 2015). With HRQoL described by Gotay and Moore (1992) as “…a state of wellbeing which is a composite of two components: 1) the ability to perform everyday activities which reflects physical, psychological and social wellbeing and 2) patient satisfaction with levels of functioning and the control of disease and/or treatment related symptoms”, identifying the impact of narcolepsy on HRQoL should be a key research goal. Despite being investigated in numerous studies, no formal systematic review and meta-analysis has been conducted to explore the health-related quality of life (HRQoL) in people with narcolepsy. Consequently, this review aimed to systematically review the literature appraising HRQoL in people with narcolepsy, provide pooled mean scores of the domains of the various HRQoL tools used in this population if possible, and compare HRQoL in people with narcolepsy to the general population and other chronic health conditions. Additional objectives of this review are to explore: i) the heterogeneity of the published studies, ii) the tools used to assess HRQoL in this population and iii) the influence of study characteristics on HRQoL.

2.2 Systematic Review Methodology

This systematic review sought to identify the HRQoL of people with narcolepsy. This review followed the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)’ statement guidelines. A study protocol which included the proposed search strategy and methodology was registered with PROSPERO (Appendix I), the international prospective registry of systematic reviews database in April 2020 (Identification number: CRD42020156036) and this review was published in the Journal of Sleep Research (Tadrous et al., 2021) (Appendix II).

2.2.1 Eligibility Criteria

The target population for this review was people with narcolepsy recruited from the general population, primary care or secondary care settings. Observational studies (case–control, cohort and cross-sectional) and experimental studies (randomised control trials, pre-post design, quasi-experimental) were deemed eligible if they assessed HRQoL in people with narcolepsy using a validated HRQoL questionnaire. HRQoL has been defined as “a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual’s ability to live a fulfilling life. However, more specifically HRQOL is a measure of the value assigned to the duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy” Ahmed and Andrich (2015). Articles were deemed ineligible for inclusion if they were case-series, case-reports, expert opinion or consensus statements; or duplicate studies that utilised the same participant data. Studies were required to provide a measure of central tendency such as mean(SD) or median (IQR) for each domain of their chosen HRQoL tool to be eligible for inclusion for each respective meta-analysis. Articles were restricted to those published in English; however, no limitation was placed on the publication year of articles.

2.2.2 Data Sources and Search Strategy

In collaboration with a senior medical librarian with specialist skills in systematic review searching (DM), a comprehensive search strategy was developed. The search encompassed four electronic databases: CINAHL, EMBASE, Medline (OVID) and Web of Science. The terms searched consisted of keywords and subject headings that were adapted for each database and can be divided into three categories: i) the condition (e.g. 'narcolepsy', 'narcolepsy type 1', 'narcolepsy type 2', 'narcolepsy with cataplexy') ii) health-related quality of life (quality of life', 'quality of life assessment', 'HRQoL'), and iii) HRQoL tools (e.g. 'Short Form 36, 'European Quality of Life 5 Dimensions Visual Analogue Scale', 'functional outcome of sleep questionnaire'). The reference lists of articles identified in the initial search were scanned to identify any studies potentially missed. The search strategy can be found in Appendix III.

2.2.3 Selection of Eligible Studies

Articles were retrieved and deduplicated. Titles and abstracts were screened to determine their eligibility for inclusion by two researchers (RT and JB). Inter-rater disagreements were resolved through careful re-examination and discussion of the article between reviewers until a consensus was reached. The full texts of the potentially eligible studies were retrieved and independently assessed by both reviewers (RT and JB) to determine eligibility for inclusion in the final analyses. A similar method of addressing disagreements between researchers was applied for the full-text screening phase.

2.2.4 Data Extraction and Risk of Bias Assessment

Primary data extraction was conducted by RT, with JB examining the articles independently to reduce bias. Two researchers (RT and JB) independently appraised the risk of bias of included studies, with disagreements resolved through discussion between researchers until a conclusion was reached. A modified version of the Joanna Briggs Institute Checklist for Analytical Cross Sectional Studies (Moola et al., 2017) was utilised to assess the risk of bias of included studies (Appendix IV). This modified tool utilised the following five domains to assess bias: i) sample, ii) subjects and setting, iii) objective measures of disease, iv) outcome measured and v) statistical analysis. Any discrepancies were resolved through discussion and review of the original article. If included articles were longitudinal or follow-up studies, baseline HRQoL data were selected for analysis.

2.2.5 Statistical Analysis

As high levels of heterogeneity were identified between studies, random-effects meta-analyses with 95% confidence intervals (CI) using Comprehensive Meta-Analysis were employed. Statistical heterogeneity was determined using I^2 values, with values nearing 25%, 50%, and 75% representing low, moderate and high heterogeneity, respectively (Higgins et al., 2003). Meta-analyses were conducted for each domain of the SF-36, and the utility and VAS scores of the EQ5D, with HRQoL questionnaires that were unable to meta-analysed being discussed in a narrative summary. Two separate meta-analyses were conducted for the physical (PCS) and mental (MCS) component summaries for the SF36, respectively. The first meta-analyses included only studies which provided calculated PCS and MCS values and their standard deviations. The second meta-analysis utilised the formula outlined by Taft et al. (2001) to calculate the PCS and MCS values from the domain scores when summary scores were not provided. Standard deviations for the PCS and MCS were imputed according to the process outlined by Furukawa et al. (2006). The impact of study variables and characteristics on HRQoL was assessed using Spearman's Correlation analyses with adjusted r^2. The HRQoL of people with narcolepsy was compared against normative SF36 values obtained the US (Ware et al., 1993), UK (Jenkinson et al., 1993), France (Audureau et al., 2013) and Norway (Ribu et al., 2007). Data from people with narcolepsy was plotted in a graph alongside data from people with epilepsy (Hermann et al., 1996), multiple sclerosis (Hermann et al., 1996), diabetes (Ribu et al., 2007), and hypertension (Kusek et al., 2002).

2.3 Systematic Review Results

2.3.1 Study Screening

The search strategy yielded 5706 articles, and following deduplication, 3399 unique articles had their titles and abstracts assessed for eligibility. From these articles, 3337 articles were deemed ineligible and excluded. The full texts of the remaining 61 articles were screened to determine eligibility for inclusion, and 31 were excluded; with 24 being published abstracts, three duplicate data sets, three utilising ineligible outcome measures and one study which assessed people without a formal diagnosis of narcolepsy. The remaining 30 articles were included in a descriptive synthesis, of which 17 articles were included in the SF36 meta-analysis, and five in the EQ5D meta-analysis. Fig. 1 shows the study selection process.

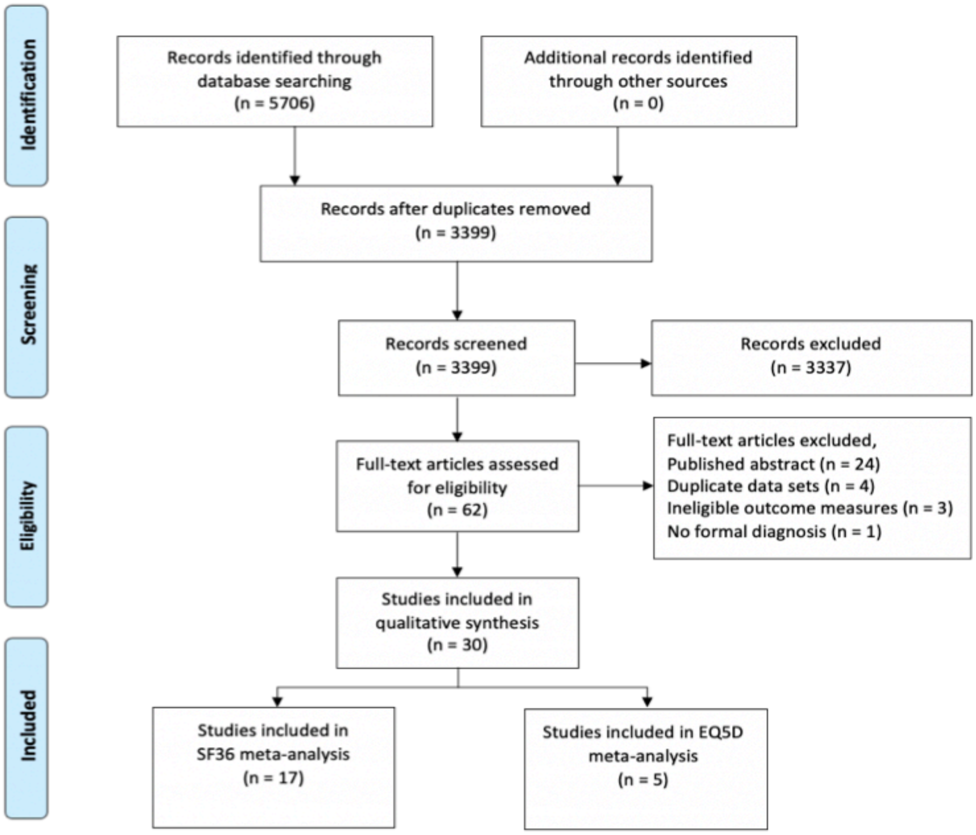


Figure 2: Flow Diagram of Studies Screened for Eligibility

2.3.2 Characteristics of included Studies

The characteristics of the included studies are outlined in Table 1. The 30 reviewed studies represent a total sample of 4600 people with narcolepsy, of which 54.31% were female (n=2498). The average number of participants in each study ranged from 15-558, with a mean of 153 participants in the included studies. The mean age of all participants was 40.8 years, with a 95% confidence interval ranging from 37.12-44.46 years. The 30 included studies originated from 13 different countries (Table 1). Studies were predominantly based in North America and Europe (80.00%), and approximately one-third of studies (n=8) were published in the United States (Becker et al., 2004, Beusterien et al., 1999, Bogan et al., 2017, Emsellem et al., 2020, Flores et al., 2016, Kapella et al., 2015, Mitler et al., 2000, Weaver and Cuellar, 2006). Four studies were published in France (Dauvilliers et al., 2009, 2011, 2017, 2019) and four in Italy (Vignatelli et al., 2004, 2011, Ingravallo et al., 2008, Ingravallo et al., 2012). Additionally, three studies were published in Japan (Kayaba et al., 2018, Ozaki et al., 2008, 2012). Only one study was published from each of the remaining countries (Table 1).

2.3.3 HRQoL Measurement Tools

A total of seven different questionnaires (SF8, SF12, SF36, EQ5D, WHOBREF (World Health Orgaisation Quality of Life-BREF), WHO-5 (World Health Organisation – Five Wellbeing Index) and, FOSQ) were utilised in the 30 included studies to assess HRQoL in this population. Of these questionnaires, six of these were generic, and one was a sleep-disorder-specific HRQoL questionnaire. The most frequently used questionnaire was the Short-Form 36, which was utilised in 22 of the 30 studies (Table 1). The EQ5D was used to assess HRQoL in six studies (Dauvilliers et al., 2017, 2019, Dodel et al., 2007, Emsellem et al., 2020, Ingravallo et al., 2012, Kovalska et al., 2016), and the FOSQ which was used in five studies (Dauvilliers et al., 2011, Kapella et al., 2015, Emsellem et al., 2020, Teixeira et al., 2004, Weaver and Cuellar, 2006). The remaining questionnaires were only used in one study each, respectively (Table 1).

2.3.4 Study Designs

A total of 22 studies utilised a cross-sectional design to assess HRQoL (Table 1), making it the most common method to assess HRQoL in this population. Studies by Weaver and Cuellar (2006), (Beusterien et al., 1999) and (Emsellem et al., 2020) utilised a multicentre, randomised, placebo-controlled design for their studies. Cohort studies were conducted by Becker et al. (2004), and Vignatelli et al. (2011). The latter study was the only study which incorporated a longitudinal design in this population, as it followed-up with participants five years after the initial study conducted by Vignatelli et al. (2004). The remaining study designs were only used in individual studies and are shown in Table 1.

Author	Year	Country	Study Type	Industry Funding	Sample Size	M/F	Age	Instrument	Quality Score	Comparison Groups/ Control
Becker	2004	America	Cohort Study	Yes	151	70/81	39.00 (18-68)	SF36	4/5	No Control Group
Beusterien	1999	America	RCT	NR	481	251/307	42	SF36 with additional scales	3/5	Placebo Control
Bogan	2017	America	Post Hoc Analysis	Yes	228	79/149	40.50 (±15.30)	SF-36,	4/5	Placebo Control
Campell	2011	New Zealand	Cross-Sectional	No	54	20/34	54.70 (±18.30)	SF36	3/5	No Control Group
Daniels	2001	United Kingdom	Cross-Sectional	No	305	120/185	56.00 (18-89)	SF36	3/5	No Control Group
Dauvilliers	2009	France	Cross-Sectional	Yes	492	238/254	41.64 (±16.53)	SF36	5/5	No Control Group: Compared NT1, NT2, and IH
Dauvilliers	2011	France	Cross-Sectional	Yes	67	31/36	44.8% <40years; 55.2% >40 years	SF36, FOSQ	5/5	Compared to Matched Controls
Dauvilliers	2017	France	Cross-Sectional	NR	175	104/71	41.50 (±17.36)	EQ5D	4/5	Compared Drug-Free and Treated Patients
Dauvilliers	2019	France	Cross-Sectional	NR	39	22/17	39.45 (±18.20)	EQ5D	4/5	No Control Group: Compared IH to NT1
David	2012	Portugal	Cross-Sectional	NR	51	26/25	43.40 (±15.30)	SF36	4/5	Compared to Population Norms
Dodel	2007	Germany	Cross-Sectional	NR	75	46/29	48.90 (±15.20)	SF36, EQ5D	4/5	Compared to Population Norms
Droogleever Fortuyn	2012	Netherlands	Cross-Sectional	NR	80	46/34	48.3 (±14.70)	SF36	3/5	No Control Group Compared Fatigued vs Non-Fatigued
Emsellem	2020	America	RCT	Yes	231	82/154	36.23 (±13.20)	SF36, EQ5D, FOSQ	4/5	Placebo Control
Ervik	2006	Norway	Cross-Sectional	NR	77	16/54	53.0 (±17.40)	SF36	5/5	No Control Group
Flores	2016	America	Cross-Sectional	Yes	437	219/218	46.70 (±16.40)	SF36 PCS and MCS	3/5	Compared to population norms
Ingravallo	2008	Italy	Cross-Sectional	No	15	9/6	48.70 (±18.80)	SF36 PCS and MCS	5/5	No Control Group
Ingravallo	2012	Italy	Cross-Sectional	NR	100	51/49	37.10 (18—65)	EQ5D	3/5	Compared to population norms
Kapella	2015	America	Cross-Sectional	No	122	27/95	27.10 (±5.00)	SF36, FOSQ	3/5	Acquaintance Approach for control group
Kayaba	2018	Japan	Cross-Sectional	No	39	20/119	24.60 (±8.30)	SF36 PCS and MCS	4/5	Compared to BIISS and DSPD
Kovalská	2016	Czech Republic	Case-Control	No	42	18/24	71.86 (±7.45)	VAS EQ5D	5/5	Age and gender matched controls
Mitler	2000	America	Cross-Sectional	No	478	220/258	42.00 (±13.0)	SF36	4/5	No Control Group
Ozaki	2008	Japan	Cross-sectional	No	55	20/35	30.29 (±10.59)	SF36	5/5	Treated vs Drug Naïve
Ozaki	2012	Japan	Cross-sectional	No	131	71/63	32.21 (±8.68)	SF36	5/5	Treated vs Drug Naïve
Rovere	2008	Brazil	Cross-sectional	No	40	12/28	41.85 (±14.5)	WHOQol-Bref	3/5	Control group present
Sarkanen	2016	Finland	Cross-sectional	NR	51	25/26	NR	Who-5 Well-Being Index	4/5	Compared to NT1
Song	2019	South Korea	Cross-sectional	No	63	43/20	27.03 (±9.29)	K-SF36	5/5	No Control Group
Teixeira	2004	Scotland	Cross-sectional	No	49	30/19	47.00 (±18.00)	SF36, FOSQ	5/5	Untreated OSAHS and CPAP treated OSAHS
Vignatelli	2004	Italy	Cross-sectional	No	108	62/46	43.20 (±16.40)	SF36	5/5	Compared to population norms
Vignatelli	2011	Italy	5-Year Prospective Cohort	No	54	42/12	48.00 (±18.40)	SF36	5/5	5 year follow up
Weaver	2006	America	RCT	Yes	228	79/149	40.50 (±15.30)	FOSQ	5/5	Placebo Control

Abbreviations
BISS = Behaviourally Induced Insufficient Sleep Syndrome
DSPD = Delayed Sleep Phase Disorder
FOSQ = Functional Outcome of Sleep Questionnaire
IH = Idiopathic Hypersomnia
SF36 = Short Form 36
KSF36 = Korean Short Form 36
NT1 = Type 1 Narcolepsy
NT2 = Type 2 Narcolepsy
OSAHS = Obstructive Sleep Apnoea Hypopnoea Syndrome

Table 1: Study Characteristics

2.3.5 Quality Assessment Risk of Bias

Quality assessment of the included studies can be found in Table 3. The appraisal scores for the included studies ranged from 3–5, with articles successfully providing sufficient information for four of the five domains on average. Only 12 studies scored the maximal possible score of 5, and 10 scoring 4/5. Inclusion criteria was the poorest performing section, with 13 of the 30 articles failing to clearly state the inclusion criteria for their study (Table 3).

Table 3: Quality Appraisal using the JBI Checklist for Analytical Cross Sectional Studies

Study ID	Inclusion Criteria	Subjects and Setting	Objective Measures Disease	Outcomes Measures	Statistical Analysis
Becker et al. (2004)	Yes	Unclear	Yes	Yes	Yes
Beusterien et al. (1999)	Unclear	Unclear	Yes	Yes	Yes
Bogan et al. (2017)	Yes	Unclear	Yes	Yes	Yes
Campbell et al. (2011)	Unclear	Yes	No	Yes	Yes
Daniels et al. (2001)	Unclear	Yes	Unclear	Yes	Yes
Dauvilliers et al. (2009)	Yes	Yes	Yes	Yes	Yes
Dauvilliers et al. (2011)	Unclear	Yes	Yes	Yes	Yes
Dauvilliers et al. (2017)	Unclear	Yes	Yes	Yes	Yes
Dauvilliers et al. (2019)	Yes	Yes	Yes	Yes	Yes
David et al. (2012)	Unclear	Yes	Yes	Yes	Yes
Dodel et al. (2007)	Unclear	Yes	Yes	Yes	Yes
Droogleever Fortuyn et al. (2012)	Unclear	Unclear	Yes	Yes	Yes
Emsellem et al. (2020)	Yes	Unclear	Yes	Yes	Yes
Ervik et al. (2006)	Yes	Yes	Yes	Yes	Yes
Flores et al. (2006)	Yes	Unclear	No	Yes	Yes
Ingravallo et al. (2008)	No	Unclear	Yes	Yes	Yes
Ingravallo et al. (2012)	Yes	Yes	Yes	Yes	Yes
Kapella et al. (2015)	Unclear	Yes	Unclear	Yes	Yes
Kayaba et al. (2018)	Unclear	Yes	Yes	Yes	Yes
Kovalská et al. (2016)	Yes	Yes	Yes	Yes	Yes
Mitler et al. (2000)	Yes	Unclear	Yes	Yes	Yes
Ozaki et al. (2008)	Yes	Yes	Yes	Yes	Yes
Ozaki et al. (2012)	Yes	Yes	Yes	Yes	Yes
Rovere et al. (2008)	Unclear	Unclear	Yes	Yes	Yes
Sarkanen et al. (2015)	Unclear	Yes	Yes	Yes	Yes
Song et al. (2019)	Yes	Yes	Yes	Yes	Yes
Teixera et al. (2004)	Yes	Yes	Yes	Yes	Yes
Vignatelli et al. (2004)	Yes	Yes	Yes	Yes	Yes
Vignatelli et al. (2012)	Yes	Yes	Yes	Yes	Yes
Weaver et al. (2006)	Yes	Yes	Yes	Yes	Yes

2.3.6 Impact on HRQoL as measured by the SF36

The pooled mean results of the SF36 domains are reported with 95% confidence intervals in Table 2. From the obtained results, the mental domains of the quality of life in people with narcolepsy are more affected than the physical domains. Both the imputed (42.98), and non-imputed (45.87) MCS were lower than the imputed (45.91) and non-imputed (49.32) PCS (Table 2). The most affected SF36 domains were Vitality (42.01) and Physical Role Limitations (45.99), and the least affected domains were Physical Functioning (67.84) and Bodily Pain (64.19) (Table 2).

2.3.7 Associated Study Variables

Spearman's Correlation analyses with adjusted r^2 values were used to assess the factors associated with HRQoL and included study quality, sample size, publication year, the proportion of female participants, mean participant age (Table 3). Age was shown to have a positive correlation on physical functioning (r^2= 0.608, p=0.05), physical role limitations (r^2= 0.643, p=0.05), bodily pain (r^2= 0.651, p=0.05), emotional role limitations (r^2= 0.706, p=0.05), and social functioning (r^2= 0.811, p=0.01). Similarly, publication year was negatively correlated with physical functioning (r^2= -0.748, p=0.01), general health (r^2= 0.0723, p=0.01), and social functioning (r^2= -0.603, p=0.05). This finding implies that reported HRQoL has improved throughout the years. With the exception of the mental health and physical role limitations, weak negative correlations were identified between the percentage of female participants and the remaining domains of the SF36.

Table 3: Meta-analysed SF36 results and associated study variables

	PF	**RP**	**BP**	**GH**	**PCS**	**PCSI**	**V**	**SF**	**RE**	**MH**	**MCS**	**MCSI**
Pooled Mean	67.84	45.99	64.19	53.59	48.32	45.91	42.01	55.66	55.22	58.71	45.47	42.98
95% CI	59.26-76.42	40.80-51.17	56.87-71.50	48.12-59.05	44.45-52.20	43.01-48.81	37.22-46.79	46.56-64.75	48.79-61.66	52.14-65.27	39.97-50.97	39.02-46.95
Heterogeneity I^2 %	99.58	95.76	98.87	98.19	99.10	98.89	98.15	99.15	97.41	98.83	99.43	99.11
Correlators												
Sample Size	-0.217	-0.566	-0.154	0.091	-0.310	0.132	-0.434	-0.273	-0.119	**1.000****	-0.600	-0.288
Mean Age	**0.608***	**0.643***	**0.671***	0.245	-0.168	0.195	0.392	**0.811****	**0.706***	-0.497	-0.119	0.436
% Female	-0.448	0.021	-0.203	-0.503	-0.466	-0.327	-0.238	-0.203	-0.385	0.028	-0.285	-0.395
Publication Year	**-0.748****	0.035	**-0.638***	**-0.0723****	0.000	-0.210	0.007	**-0.603***	-0.473	-0.063	-0.142	0.330

* = Correlation is significant at p =0.05	**=Correlation is significant at p=0.01
CI = Confidence Interval	V = Vitality
PF= Physical Functioning	SF = Social Functioning
RP = Physical Role Limitations	RE = Emotional Role Limitations
GH = General Health	MH = Mental Health
PCS = Physical Component Summary	MCS = Mental Component Summary
PCSI = Physical Component Summary (Imputed Standard Deviations)	MCSI = Mental Component Summary (Imputed Standard Deviations)

2.3.8 Comparison of HRQoL General Population Norms and Other Chronic Health Conditions

The mean HRQoL for each domain of the SF36 was plotted against the general population norms for the US (Ware et al., 1993), UK (Jenkinson et al., 1993), France (Audureau et al., 2013) and Norway (Ribu et al., 2007) in Figure 3. The results of this comparison demonstrate that the HRQoL of people with narcolepsy is considerably impaired when compared to the general population, particularly the physical role limitations, social functioning and emotional role limitations domains.

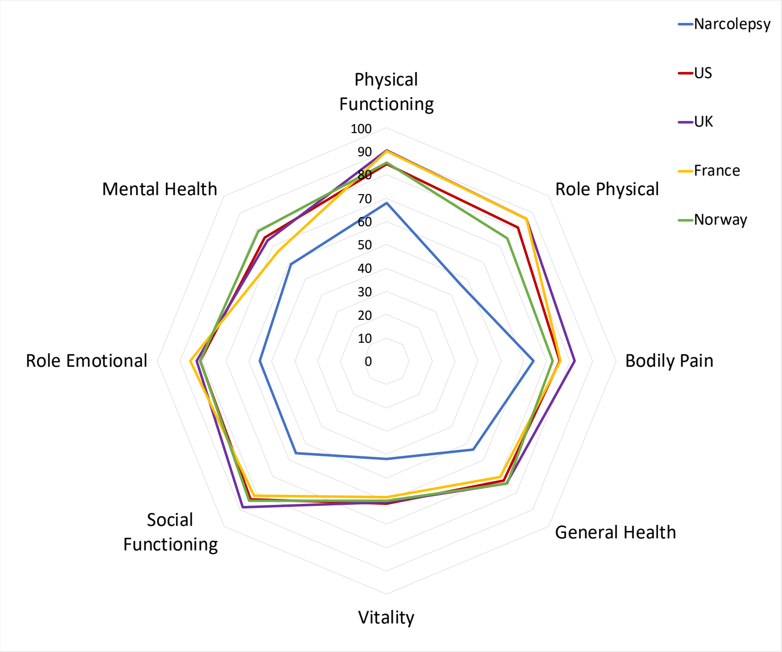


Figure 3: SF36 Values Compared to General Population Norms

Figure 4 compares the SF36 scores of people with narcolepsy to other chronic health conditions including epilepsy (Hermann et al., 1996), multiple sclerosis (Hermann et al., 1996), diabetes (Ribu et al., 2007), and hypertension (Kusek et al., 2002). People with narcolepsy experience consistently lower levels of mental health, emotional role limitations, social functioning and bodily pain when compared to the aforementioned chronic health conditions. When compared to epilepsy, diabetes and hypertension, people with narcolepsy scored lower in all eight domains of the SF36. With the exception of physical functioning, physical role limitations, and vitality, people with narcolepsy scored lower than people with multiple sclerosis in the remaining five SF36 subscales (Figure 4).

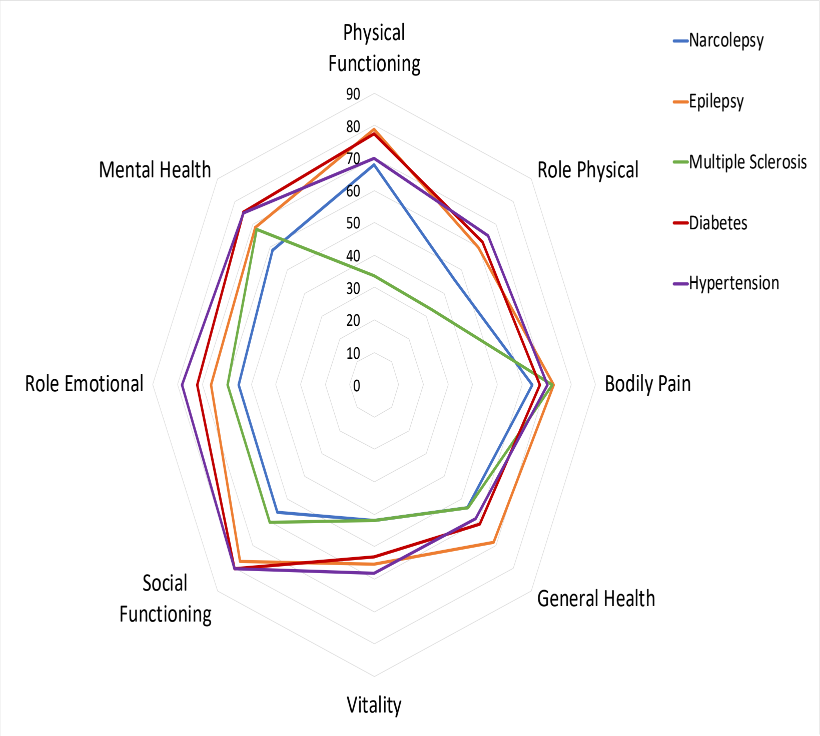


Figure 4: SF36 Values Compared to Chronic Conditions

2.3.9 Other HRQoL Questionnaires

EQ5D: The mean utility score obtained from the analysed studies was 0.85 (0.82-0.88, 95% CI). Additionally, the mean score obtained from the visual analogue scale (VAS) of the EQ5D was 66.63, with the 95% confidence interval ranging from 61.83-71.43. Figure 5 compares the VAS scores of the sample with narcolepsy to population norms of the US, UK, and France (Szende et al., 2014).

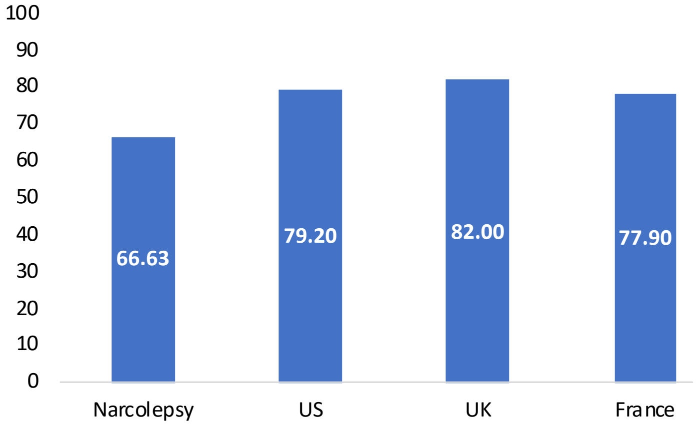


Figure 5: EQ5D VAS Scores Compared to General Population Norms

FOSQ: The FOSQ was utilised by Dauvilliers et al. (2011), Kapella et al. (2015), Emsellem et al. (2020), Teixeira et al. (2004), Weaver and Cuellar (2006) to assess HRQoL in this population. Studies by Dauvilliers et al. (2011) and Weaver and Cuellar (2006) were excluded from the analysis as they failed to report their baseline values for the FOSQ domains. The results from Kapella et al. (2015), and Teixeira et al. (2004) identified that Activity Levels (2.27) and Vigilance (2.34) were the most affected quality of life domains, and Sexual Wellbeing (3.0) and Social Outcomes (2.71) were the least affected domains. The total score obtained from Kapella et al. (2015) (13.3) was considerably higher than that of Teixeira et al. (2004) (9.5). However, the study by Teixeira et al. (2004) did not assess Sexual Wellbeing, and when this domain is excluded from the results obtained by Kapella et al. (2015), their adjusted total score becomes 10.3. The FOSQ-10, a concise version of the FOSQ, was utilised by Emsellem et al. (2020). The total scores reported ranged from 11.4-12.2, with a mean of 11.675 (3.21).

Concise Short Forms: The SF8 and SF12 were utilised by Kayaba et al. (2018) and Flores et al. (2016), respectively. The study by Flores et al. (2016) failed to report the SF12 results obtained by their study. The study by Kayaba et al. (2018) reported the component summaries obtained by their participants. They identified that the physical wellbeing (50.7 ± 6.4) was less severely affected than mental wellbeing (44.8 ± 9.6), as measured by the PCS and MCS, respectively.

WHO Questionnaires: The WHOQOL-Bref and WHO-5 were used by Rovere et al. (2008), and Sarkanen et al. (2016) to assess HRQoL in their respective studies. The results obtained by Rovere et al. (2008) identified that Physical Wellbeing is the most affected HRQoL domain (48.93 ± 15.67), followed by Environmental factors (50.16 ±15.32). Conversely, Social Wellbeing (60.83 ± 17.11) and Psychological Wellbeing (56.04 ± 14.74) were the least affected HRQoL domains in this population. The results obtained from Sarkanen et al. (2016) failed to report baseline values for the WHO-5, only reporting the total scores obtained upon the initial (45.5 ± 24.8) and follow-up visit (48.0 ± 19.3).

2.4 Systematic Review Discussion

This was the first systematic review and meta-analyses to comprehensively assess the impact of narcolepsy on HRQoL. This review identified that narcolepsy negatively impacts HRQoL and that people with narcolepsy report considerably lower quality of life than general populations as well as several other chronic disease populations. Furthermore, the majority of included studies were of high quality as measured by the JBI Checklist for Analytical Cross Sectional Studies tool.

The most notably affected HRQoL domain compared to the general population was physical role limitations. However, mental domains were also considerably affected, in particular, social functioning and emotional role limitations. Furthermore, people with narcolepsy reported considerably lower HRQoL in all SF36 domains than people with diabetes, epilepsy, and hypertension. When compared to multiple sclerosis, with the exception of physical functioning (+34.34), physical role limitations (+13.29), and vitality (+0.11), people with narcolepsy scored lower than in the remaining five SF36 subscales. These comparisons serve to highlight the high symptom burden associated with narcolepsy.

The finding that people with narcolepsy report poorer quality of life than people with epilepsy is consistent with the findings of the study conducted by (Broughton et al., 1984). The comparison between narcolepsy and epilepsy is particularly notable as both neurological conditions cause individuals to experience episodic attacks and excessive daytime sleepiness to some extent. However, EDS in people with narcolepsy is a consistent feature as part of their underlying condition, whilst EDS in people with epilepsy may be as a result of medications, uncontrolled seizures or a comorbid sleep disorder (Broughton et al., 1984). More appropriate comparisons are limited until similar reviews are conducted in other disorders of hypersomnolence.

This review shows the burden that narcolepsy places on people experiencing this condition. In particular, the MCS scores (42.98) were lower than those of the PCS (45.91), suggesting that narcolepsy has a more significant impact on the mental wellbeing than the physical wellbeing of people with narcolepsy. However, the most affected HRQoL domains primarily related to physical wellbeing, as physical role limitations (45.99) and vitality (42.01) were the most affected SF36 domains, and activity levels (2.27) were the most affected FOSQ domain. These results highlight that impairment with daily activities, fatigue and reduced energy levels are central to the lived experience associated with narcolepsy. A possible explanation for this finding is the interrelationship between physical performance and mental wellbeing in people with narcolepsy suggested by Morse and Sanjeev (2018), with less physical activity in people with narcolepsy being linked to poorer mood (Bruck et al., 2005). This population generally has reduced opportunities to exercise due to time constraints related to sleepiness and social isolation (Kapella et al., 2015), and considerably lower physical activity has been reported in people with narcolepsy than the general population (Parmar et al., 2019). A vicious cycle can be established with sedentary behaviour promoting increased sleepiness severity (Golden and Lipford, 2018), and this increased symptom burden further reducing habitual levels of physical activity and HRQoL (Matoulek et al., 2017). The impact of physical activity levels on physical and mental wellbeing in this population warrants further exploration.

This review identified significant negative correlations between date of publication and the physical functioning (p=0.01), general health (p=0.01) and social functioning (p=0.05) domains of the SF36. This finding may imply that improved treatment options and knowledge about narcolepsy by medical professionals can have positive effects on HRQoL in people with narcolepsy. Similarly, this review identified that older age of symptom onset was negatively associated with physical role limitations, physical functioning and vitality (p=0.01). In a study by Ingravallo et al. (2012), people with the onset of narcolepsy occurring later in life viewed their health as worse, achieved lower educational levels and experienced more employment problems than those with onset earlier in life. Possible explanations for the relationship between later onset and poorer HRQoL may include reduced habituation to their condition. The effect of ageing on HRQoL, however, remains ambiguous. Increasing age was found to be positively associated with physical functioning, physical role limitations, bodily pain, emotional role limitations (p=0.05), and social functioning (p=0.01). However, the findings from studies by Vignatelli et al. (2004) and Vignatelli et al. (2011) showed that there was no significant difference in SF36 domain scores and only slight declines in the component summaries. A possible explanation for the positive correlation associated with age is that as this population ages, they become more accepting of their condition. Further longitudinal research is necessary to evaluate the long term impact of ageing on HRQoL in this population.

This review highlighted that there was diversity in HRQoL tools utilised, with a total of six tools employed. However, there was some agreement on the tools used to measure HRQoL in people with narcolepsy as over two-thirds of the included studies utilised the SF36 (n=22). Only five studies utilised the FOSQ, a sleep-disorder-specific tool, and of which, four utilised a combination of generic and sleep-disorder-specific tools. Although the SF36 is a comprehensive generic HRQoL tool, it may lack the specificity to assess the subtle aspects of the HRQoL imposed by narcolepsy. Similarly, although the FOSQ may be a sleep-disorder-specific tool, it is not a narcolepsy-specific tool and similar issues to the SF36 may arise. The study by Beusterien et al. (1999) reported that they utilised supplemental scales in an attempt to assess common issues in narcolepsy, namely measures of overall health perceptions, driving limitations, and social support. To the authors' knowledge, this was the only study to incorporate these additional scales to assess HRQoL in people with narcolepsy. This review has identified the considerable need for the development of a psychometrically robust narcolepsy-specific tool to assess HRQoL in this population. The combination of a generic and a condition-specific HRQoL tool is recommended to assess HRQoL in this population, as this would enable comparison with other health conditions, and detection of sleep-disorder-specific HRQoL impairments.

Several limitations pertained to this review. Firstly, this review excluded articles that were not published in English or grey literature due to time constraints. The decision to include the baseline values obtained from randomised control trials may have limited this review, as the obtained sample may not be wholly representative of people with narcolepsy due to the strict inclusion criteria that are often associated with such trials. Additionally, participants would likely have been on different medication regimens, and as a result, the heterogeneity of the overall sample must be considered when interpreting the results of this review. Furthermore, the certainty of participants' diagnosis of narcolepsy must be considered, particularly for earlier studies, as their large and heterogenous samples may have included individuals with similar conditions such as insufficient sleep syndrome or idiopathic hypersomnia. Another potential limitation of this review was the substantial number of included studies that failed to report the PCS and MCS scores for the SF36 (n=8). Although these summary scores could be calculated from the domain scores provided, the standard deviation of these scores could not be calculated, and as a result, standard deviations had to be imputed according to the formula described by Furukawa et al. (2006). Comparable methods were adopted by similar systematic reviews such as the reviews conducted by Matcham et al. (2014) and Gu et al. (2019). Additionally, both the imputed and non-imputed values of the component summaries were reported to address this limitation. Another possible limitation of this study included the relatively small sample sizes of the chronic conditions used to compare against the SF36 domain scores obtained by people with narcolepsy. Consequently, the results of this comparison must be cautiously interpreted. As the majority of studies (n=26) did not provide subgroup results, the comparison between type 1 and type 2 narcolepsy was unable to be made. Similarly, the relationship between employment status and HRQoL could not be explored as the nine studies which reported employment status used different HRQoL tools.

Strengths of this review include that PRISMA guidelines were closely followed to ensure that our search strategy captured the complete and relevant published literature. Furthermore, studies were evaluated using a standardised measure, and included studies were generally high quality as measured by the JBI tool.

2.5 Systematic Review Conclusion

This is the first review that has attempted to systematically assess the impact of narcolepsy on HRQoL. HRQOL is an important endpoint in narcolepsy research. Given the reduced HRQOL in people with narcolepsy, its measurement can aid the assessment of treatment response and can help guide the allocation of resources within the clinical setting. The results of this review demonstrated that people with narcolepsy experience substantial impairment of their mental and physical wellbeing compared to general populations as well as other chronic disease populations, but a more consistent approach is needed to explore the effect of narcolepsy on HRQoL and for higher quality trials to be conducted int this population. The possible usefulness of a validated, patient-reported measure specific for narcolepsy and its symptoms should be evaluated to measure the true impact of this disease. Future research should explore the effects of ageing on HRQoL in people with narcolepsy, HRQoL differences in type 1 and type 2 narcolepsy, and predictors of HRQoL in this population.

Chapter 3: Profiling Physical Performance Variables in an Out-Patient Adult Population with Narcolepsy

3.1 Study Justification

Physical function is described by (Campbell et al., 2013) as "one's ability to execute daily activities with optimal fitness, endurance, and strength with the management of disease, fatigue, stress and reduced sedentary behaviour". Physical function can be defined as a multidimensional construct containing the components cardiorespiratory endurance, muscular strength, muscular endurance, flexibility and body composition (Britton et al., 2020). Physical function is routinely measured objectively using physical performance tests and monitoring physical activity (van Lummel et al., 2015). Evident from the systematic review and meta-analysis was the significant burden narcolepsy exerts on physical wellbeing, as physical role limitations and vitality were the most affected domains of HRQoL. With significant correlations identified between HRQoL and symptom severity (Dauvilliers et al., 2017), the low values for the physical domains of HRQoL in this cohort warranted further investigation.

The relationship between physical functioning and symptom severity in people with narcolepsy is not fully understood and is likely complex. In a study by Matoulek et al. (2017), poorer cardiorespiratory fitness was shown to correlate with increased severity of excessive daytime sleepiness, and the frequency of cataplexy attacks. In children with narcolepsy, physical activity was shown to correlate with lower body mass index (BMI), increased night-time sleep duration, higher sleep quality, and reduced frequency of napping (Filardi et al., 2018). Furthermore, considerably lower physical activity has been reported in people with narcolepsy than the general population (Parmar et al., 2019), and this reduced physical activity has been shown to correlate with depressive symptoms in people with narcolepsy (Bruck et al., 2005). In the general population, a bidirectional relationship between exercise and sleep has been identified, with exercise demonstrating its' ability to be utilised as an effective nonpharmacological treatment option for disturbed sleep, and poor sleep contributing to lower physical activity levels (Kline, 2014).

However, little is known about the physical performance of people with narcolepsy as this is a cohort that is not commonly encountered by physiotherapists. In other populations with chronic conditions, profiling physical performance variables such as strength, cardiopulmonary fitness and physical activity can provide early indications that an individual is at increased risk of functional decline, hospitalisations and mortality (Corsonello et al., 2012, Legrand et al., 2014). Profiling the physical performance of people with narcolepsy may help identify individuals that are 'at risk' and can enable the comparison between the physical performance of this cohort to that of the general population. As this is a relatively understudied population, identifying the physical performance of people with narcolepsy could help tailor exercise recommendations for this cohort and aid the exploration of how physical performance influences the quality of life and symptom severity in people with narcolepsy.

3.2 Aims and Objectives of the Study

Overall aim:

The overall aim of this study is to profile the physical performance of people with type 1 or type 2 narcolepsy that attend the Narcolepsy Clinic in St. James's Hospital as an outpatient.

Objectives:

i. To profile the following variables: cardiopulmonary fitness, muscle strength, muscle endurance, physical activity and sedentary behaviour in people with narcolepsy attending the Narcolepsy Clinic in St. James's Hospital.
ii. To determine the quality of life and symptom severity of the study population.
iii. To compare the study populations' physical performance to general population norms.
iv. To compare the study populations' quality of life to general population norms and other chronic health conditions.
v. To explore the relationship between physical performance, quality of life and symptom severity in the study population.
vi. To ascertain the study populations' priorities and concern regarding their physical health, their barriers towards physical activity and their perception of physiotherapy.

3.3 Methods

3.3.1 Study design

This study was a cross-sectional study that comprehensively profiled the physical performance of adults attending a dedicated narcolepsy outpatient clinic at St. James's Hospital, Dublin. The Narcolepsy Clinic in St James's Hospital is home to the National Narcolepsy Centre, complete with a fully equipped and state-of-the-art sleep lab. The dedicated narcolepsy team consists of a medical consultant, clinical nurse specialist and clinical nutritionist. Ethical approval for this study was obtained from the St. James's Hospital and Tallaght University Hospital Research Ethics Committee (Appendix V). This study was registered on Clinicaltrials.gov (NCT04419792, Appendix VI), and the protocol of this study was published (Tadrous et al., 2020)(Appendix VII).

3.3.2 Study population

Participants were required to meet the following eligibility criteria: aged 18 to 65 years, diagnosed with type 1 or type 2 narcolepsy based on the International Classification of Sleep Disorders third edition criteria (American Academy of Sleep Medicine, 2014) for at least six months, eligibility screened by their treating clinician, and able to understand English and follow simple instructions to enable completion of assessments. Additionally, participants were required to provide signed and informed consent to participate in the study, and for processing of their data to be eligible for participation. Individuals with sleep disorders other than narcolepsy, contraindications to moderate-intensity exercise, confirmed pregnancy, or significant psychiatric illness or cognitive impairment were excluded from participating in the study.

3.3.3 Recruitment

Potential participants were screened by their treating clinicians in advance of their scheduled clinic visit, and sent an information leaflet at least 5-7 days before their appointment if deemed eligible to participate. A follow-up call from the specialist nurse was made to answer any study-related questions. During their clinic visit, the primary study assessor (a research physiotherapist, R.T.) approached potential participants and provide additional information regarding the study. Participants were provided with a consent form and participant information leaflet (Appendix VIII).

3.3.4 Assessment Process

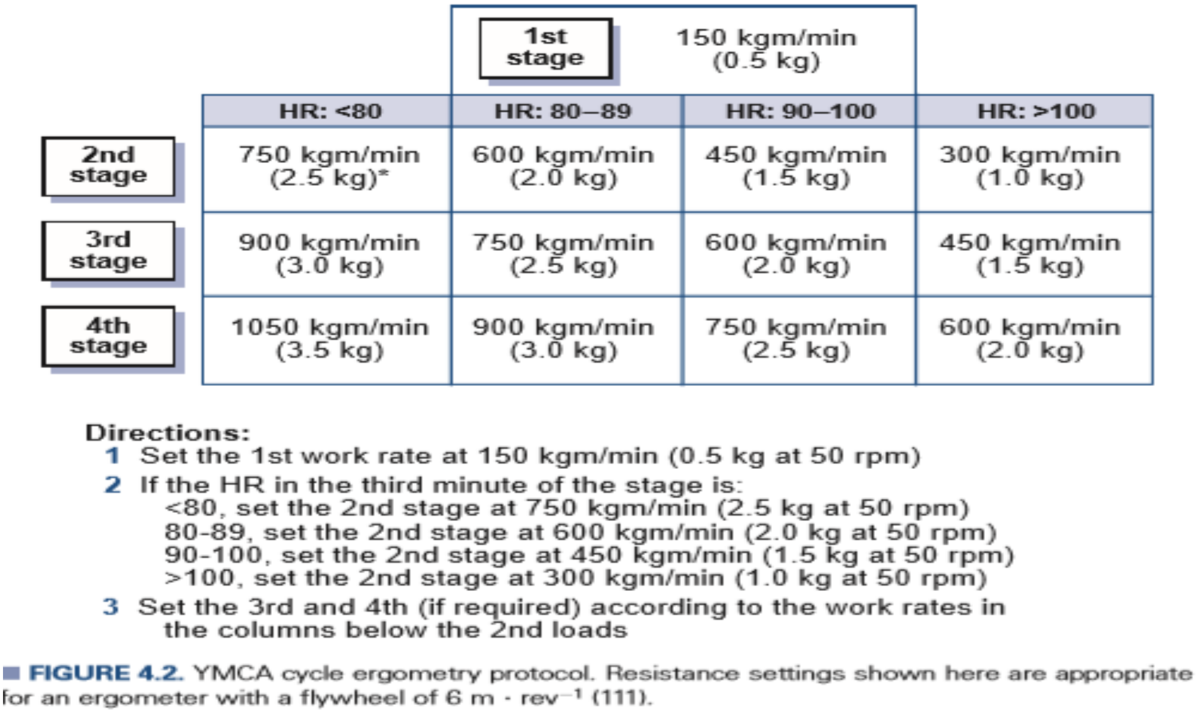
Following obtainment of consent, demographic information was gathered from participants (age, gender, narcolepsy subtype, living arrangements, employment status, highest educational achievement and medications prescribed). Participants then underwent the battery of physical performance outcome measures in the order as seen in Table 4, with all physical outcome measures completed in one assessment session. Following completion of the test battery, participants would then be qualitatively interviewed by the research physiotherapist (RT). Participants also had to complete several questionnaires that explored their symptom severity, quality of life, physical activity and sedentary behaviour (Table 4). Due to the fluctuating energy levels associated with narcolepsy (Kapella et al., 2015). participants were able to select when they wanted to complete the questionnaires, i.e. prior to their assessment (posted to their homes or in waiting area prior to clinic appointment), during the testing process (after the qualitative interview) or following the testing process (sent back via return addressed envelopes provided). Participants then received an Actigraph, were instructed on its use and provided with a return-addressed envelopes, and told to return the Actigraph following one week. The entire assessment process lasted approximately 45 minutes.

I. **Physical variables**

Participants were asked to undergo an expanded physiotherapy assessment which consists of measures of cardiovascular fitness and physical activity. The primary study assessor conducted the following test battery:

3.3.5.1 Cardiopulmonary Fitness

Cardiopulmonary fitness was assessed by the YMCA submaximal bike test to estimate VO_2 max (Golding et al., 1989). The YMCA submaximal bike test is reported to have a moderately high correlation coefficient of r = 0.79, and when used to assess cardiopulmonary fitness in a heterogeneous population, Beekley et al. (2004) found no statistical difference between the predicted VO_2 max and the criterion measure (mean difference = 1.3 $ml/kg^{-1}/min$). The YMCA protocol uses two to four three-minute stages of continuous exercise. The test is designed to raise the steady-state heart rate of the subject to between 110 beats per minute and 85% of their age-predicted maximal heart rate for at least two consecutive stages (American College of Sports Medicine, 2013).



1st stage 150 kgm/min (0.5 kg)

	HR: <80	HR: 80–89	HR: 90–100	HR: >100
2nd stage	750 kgm/min (2.5 kg)*	600 kgm/min (2.0 kg)	450 kgm/min (1.5 kg)	300 kgm/min (1.0 kg)
3rd stage	900 kgm/min (3.0 kg)	750 kgm/min (2.5 kg)	600 kgm/min (2.0 kg)	450 kgm/min (1.5 kg)
4th stage	1050 kgm/min (3.5 kg)	900 kgm/min (3.0 kg)	750 kgm/min (2.5 kg)	600 kgm/min (2.0 kg)

Directions:
1 Set the 1st work rate at 150 kgm/min (0.5 kg at 50 rpm)
2 If the HR in the third minute of the stage is:
  <80, set the 2nd stage at 750 kgm/min (2.5 kg at 50 rpm)
  80-89, set the 2nd stage at 600 kgm/min (2.0 kg at 50 rpm)
  90-100, set the 2nd stage at 450 kgm/min (1.5 kg at 50 rpm)
  >100, set the 2nd stage at 300 kgm/min (1.0 kg at 50 rpm)
3 Set the 3rd and 4th (if required) according to the work rates in the columns below the 2nd loads

■ **FIGURE 4.2.** YMCA cycle ergometry protocol. Resistance settings shown here are appropriate for an ergometer with a flywheel of 6 m · rev^{-1} (111).

Figure 6: Snapshot of YMCA submaximal cycle ergometer protocol, ACSM (2014).

3.3.5.2 Actigraphy

Physical activity and sedentary behaviour were measured objectively through the use of Actigraphy. Actigraphy is based on miniaturised acceleration sensors that translate physical motion to numeric representations (Sadeh et al., 1995). Actigraphy utilises a portable device to collect movement information over prolonged periods of time (Berry, 2012). Actigraphy is based on the concept that movement is increased during waking hours and reduced during sleep (Littner et al., 2003). The GTX3 model actigraph has strong relationships between counts per minute and VO_2 ($r = 0.810$, $p < 0.001$), and can reliably quantify physical activity when compared to oxygen consumption (Kelly et al., 2013). Participants were asked to wear the Actigraph around their waist for seven consecutive days, excluding swimming or bathing, and log the duration worn. Participants were asked to post the Actigraph and wear time log to the study assessor in stamped addressed envelopes previously provided to them. Actigraph data was downloaded and analysed using the ActiLife Software (ActiGraph Manufacturing Technology Inc., FL).

Figure 7: Actigraph Worn Around Waist

Source: Figure from Riel et al. 2016

DOI: 10.7717/peerj.2799/fig-1

Figure 8: Actigraph Device

Source: https://actigraphcorp.com/actigraph-wgt3x-bt/

3.3.5.3 Lower Body Assessments

Vertical jump height and power were measured through the countermovement jump test. The countermovement jump test correlates with sprint performance, maximal strength, and explosive-strength tests (Nuzzo et al., 2008). When compared to other jump tests, the countermovement jump test is the most reliable measure of lower-body power (Markovic et al., 2004). Furthermore, the countermovement jump test demonstrates great factorial validity through its relationship with explosive power (r = 0.87), low within-subject variation of 2.8% and high reliability with a Cronbach's alpha of 0.98 (Markovic et al., 2004). Subjects were instructed to place chalk on their dominant hand. Participants stood with their dominant shoulder about 6 inches (15 cm) from the wall and, with both feet flat on the floor, reached as high as possible with the dominant hand and made a chalk mark on the wall. They then lowered their dominant hand and performed a countermovement by quickly flexing their knees and hips, moving their trunk forward and downward, and swinging their arms backwards. During the jump, their dominant arm reached upward, and at the highest point in the jump, the participant placed a second chalk mark on the wall with the fingers of their dominant hand using a swiping motion of the fingers. The score is the vertical distance between the two chalk marks. The best of three trials was recorded to the nearest 0.5 inches or 1.0 cm (Haff and Triplett, 2015).

The isometric wall sit test is commonly used for evaluating endurance because it can be administered almost anywhere and is not complex (Tomchuk, 2011). Little equipment is necessary for the wall squat test, making it both cost-effective and accessible (Goldring et al., 2014). The intra-class correlation coefficient for the wall squat test ranges from 0.69 to 0.88 (Lubans et al., 2011). Participants were instructed to place their back flat against the wall, with their toes pointed straight out and away from the wall. When instructed to go, the participant slid their back down the wall until their knees were at a 90-degree angle. This position was maintained until exhaustion, and only one trial was performed. The participants were timed from the moment they obtained the proper test position until they could no longer maintain this position (Tomchuk, 2011).

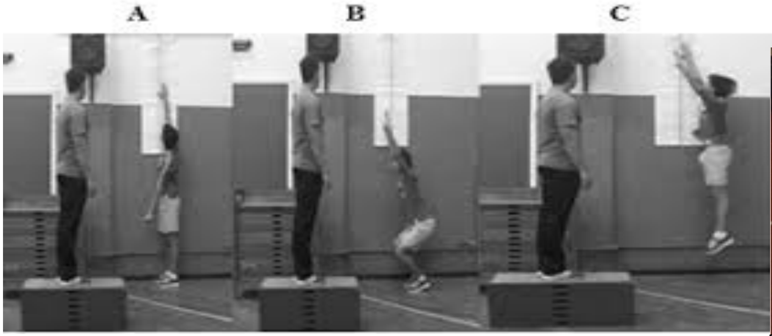


Figure 9: Countermovement Jump Test Procedure

Source: Nogueira et al. 2020, DOI:10.7752/jpes.2020.01033

Figure 10: Wall Squat Procedure

Source: Brown et al. 2013

3.3.5.4 Upper Body Assessment

Grip strength was assessed using a handheld calibrated dynamometer (JAMAR, Hatfield, PA, USA). Although the relationship is not causative, grip strength has been reported to correlate with chronic health conditions (Bohannon, 2008, Massy-Westropp et al., 2011). Low grip strength has been associated with low spinal and pelvic bone mineral density and increased risk of vertebral fractures in women (Dixon, 2005). Additionally, longitudinal studies have identified strong inverse relationships between grip strength and all-cause mortality, mortality from cardiovascular disease, respiratory disease, and cancer (Celis-Morales et al., 2018). Furthermore, grip strength has been shown to be a predictor of absolute muscular strength and endurance (Trosclair et al., 2011). The American Society of Hand Therapists recommends that the Jamar dynamometer is used as the gold standard for the assessment of grip strength (Fess et al., 1992). The Jamar dynamometer has excellent test-retest reliability (ICC = 0.822), and interrater reliability (ICC = 0.996-0.998) as reported by Mathiowetz et al. (1984), and (Lindstrom-Hazel et al., 2009), respectively. Furthermore, Jamar dynamometry has excellent concurrent validity between participant's dominant hand (ICC = 0.99) and non-dominant hand (ICC = 0.98) as reported by Bellace et al., (2000). Measurements were obtained in standardised conditions and following testing conditions as outlined by the American Society of Hand Therapists (MacDermid et al., 2015). The participants were instructed to squeeze as hard as they can for 3 to 5 seconds. The procedure was performed three times with each hand alternately, with an interval of one minute between each measurement (MacDermid et al., 2015).

Figure 11: JAMAR Handgrip Dynamometer

(URL: https://www.4mdmedical.com/jamar-plus-digital-hand -dynamometer-hand-dynamometer.html

The American College of Sports Medicine (ACSM) Push-Up test was used to assess the strength and endurance of the upper limb. The Push-up test has been described as a simple, cost-effective measure that can provide an approximation of functional status (Yang et al., 2019). Muscle strength and endurance have been shown to provide an independent protective effect for all-cause mortality and hypertension in adult males (Artero et al., 2011). Furthermore, longitudinal studies have suggested that push up capacity is inversely related to the risk of cardiovascular disease, with individuals capable of performing 11 or more push-ups having significantly reduced risk of subsequent cardiovascular events (Yang et al., 2019). The Push-Up test is highly reliable (r = 0.95 and 0.91) for predicting upper limb muscular endurance in collegiate students (Baumgartner et al., 2002). The Push-Up test has a test-retest interclass correlation coefficient of 0.95, with a 95% confidence interval of 0.85-0.99 (Ryman Augustsson et al., 2009). The maximal number of push-ups performed consecutively without rest was counted. The test was stopped when the participant strained forcibly or was unable to maintain the appropriate technique within two repetitions (American College of Sports Medicine, 2013).

Figure 12: ACSM Press Up Test Procedure

Source: Mayo Foundation for Medical Education and Research

II. **Questionnaires:**

Participants were asked to complete several questionnaires which subjectively explored the participant's perception of their physical activity levels, quality of life and symptom severity.

3.3.6.1 Health-Related Quality of Life

Health-related quality of life (HRQoL) was evaluated using the Medical Outcomes Short-Form 36 (SF36) and the functional outcomes of daytime sleepiness questionnaire (FOSQ). The SF36 (Appendix IX) is one of the most widely used scales for measuring HRQoL, and it has been used in various populations and different health conditions (Ware, 2000). The SF36 includes one multi-item scale that assesses eight health domains: Physical Functioning, Physical Role Limitations, Bodily Pain, General Health, Vitality, Social Function, Emotional Role Limitations and Mental Health. A higher score implies better health status. These eight domains can be combined into a physical component score (PCS) and mental component score (MCS) to provide a general overview of health and wellbeing (Ware and Sherbourne, 1992). The FOSQ (Appendix X) takes approximately 15 minutes to complete and measures how a person's actual daily ability to function is affected by their sleepiness. This is conceptually defined as those everyday behaviours encompassing the areas of physical, mental, and social functioning in daily life (Weaver et al., 1997). The FOSQ contains five domains: General Productivity, Social Outcome, Activity Levels, Vigilance and Sexuality/Intimacy. Domain scores can be summated and a total score can be calculated.

3.3.6.2 Symptom Severity

Symptom severity was assessed through condition-specific questionnaires such as the Epworth Sleepiness Scale (ESS) and the Narcolepsy Severity Scale (NSS). The ESS (Appendix XI) is a simple method for measuring the general level of daytime sleepiness in adults. The ESS is an eight-item measure of daytime sleepiness. Respondents report their likelihood of falling asleep in particular situations using a 4-point Likert scale. Subjects were asked to distinguish dozing behaviour from feelings of tiredness. The ESS score is the sum of eight item-scores and can range from 0 to 2, and higher scores indicate greater sleepiness; scores more than 10 suggest excessive daytime sleepiness (Johns, 1991). The NSS (Appendix XII) is a 15-item scale that assesses the clinical symptoms of narcolepsy such as EDS, cataplexy, hallucinations, sleep paralysis and disturbed night-time sleep. These symptoms were selected and validated by experts in sleep medicine, who took into account feedback from people with narcolepsy (Dauvilliers et al., 2017).

3.3.6.3 Physical Activity

Physical activity was subjectively assessed through the Physical Activity Vital Sign and Sedentary Behaviour Questionnaire. The Physical Activity Vital Sign (Appendix XIII) is a clinical assessment tool designed to gauge the moderate to vigorous physical activity levels in adults. The Physical Activity Vital Sign ascertains how many days during the past week participants performed physical activity for at least 30 minutes where their heart beats faster and their breathing is heavier than normal (Greenwood et al., 2010). The Sedentary Behaviour Questionnaire (Appendix XIV) was designed to assess the amount of time spent doing the following sedentary activities: watching television, playing computer games, listening to music, talking on the phone, doing paperwork or office work, reading, playing an instrument, doing arts and crafts, sitting and driving/riding in a car, bus, or train. These items were completed separately for weekdays and weekend days and summated to provide an estimate of weekly sedentary behaviour (Rosenberg et al., 2010).

Table 4: Test Battery of Outcome Measures

Physical Performance Tests			**Questionnaires**		
Name		**Category**	**Name**		**Category**
1.	YMCA Submaximal Bike Test	Cardiovascular Fitness	1.	Physical Activity Vital Sign	Physical Activity
2.	ACSM Push Up Test	Muscular Endurance	2.	Sedentary Behaviour Questionnaire	Sedentary Behaviour
3.	Hand Grip Dynamometry	Muscular Strength	3.	Narcolepsy Severity Scale	Symptom Severity
4.	Countermovement Jump Test	Muscular Strength	4.	Epworth Sleepiness Scale	Symptom Severity
5.	Wall Squat Test	Muscular Endurance	5.	Short Form 36	Quality of Life
6.	Actigraphy	Physical Activity Sedentary Behaviour	6.	Functional Outcomes of Sleepiness Questionnaire	Quality of Life

3.4 Qualitative Interview

A qualitative interview to explore perceptions of unmet physical health needs was carried out by the research physiotherapist (R.T) in the Physiotherapy Department in St James's Hospital. Interviews lasted approximately ten minutes, and participants were asked several open-ended questions that were audio-recorded and transcribed verbatim by the study assessor. The following questions were asked: What do you feel are your main barriers and motivators to being more physically active/exercising? Do you have any concerns with your physical health (your strength, how fit you feel) at the moment? What matters most to you at the moment? Is there anything we could do/offer to address these concerns? Have you any suggestions for us based on the tests you have just completed or anything else to add?

3.5 Thematic Analysis

Straightforward thematic analysis was completed independently by two individuals (R.T. and C.Q) and was used to identify patterns/themes in data generated from the open-ended questions (Braun and Clarke, 2006). This process consisted of six steps, with data saturation established when no new themes emerged (Fusch and Ness, 2015):

i. **Data Transcription:** Responses were audio-recorded and transcribed verbatim by the study assessor (R.T). Data was then read, re-read and initial ideas from the responses were noted.
ii. **Generating Initial Themes:** Interesting features of the data were coded using a systematic approach across the complete data set. Interesting aspects from the responses were also noted during this phase.
iii. **Searching for Themes:** Similar codes that were generated were collated into potential themes. All relevant data were grouped under these specific themes.
iv. **Reviewing Themes:** Themes were reviewed in relation to the identified codes and the entire data set. In doing so, this process generated a thematic 'map' of the analysed data.
v. **Defining and Naming Themes:** Themes were continuously analysed and refined based on specific aspects identified to create an overall story of the analysed data. Clear definitions and names were created for each theme.
vi. **Producing the Report:** Vivid and compelling extracts from responses were selected that related to the specific research questions and literature in order to produce a comprehensive report of the analysis.

3.6 Statistical Analysis

Data was entered into Excel, checked and coded. Physical performance variables of participants within this study was descriptively quantified. Normality was assessed using the Kolmogorov-Smirnov test to determine if parametric or non-parametric statistics should be applied. As all data-was non-normally distributed, only non-parametric statistics were applied. Differences between males and females was assessed using the Mann-Whitney U test. Spearman's correlation analyses was used to explore relationships between the following data:

I. Physical performance variables and sleep quality and narcolepsy severity.
II. Physical performance variables and quality of life.

The data obtained from the study was analysed using SPSS V26 software (IBM Corp, 2019). A p-value of <0.05 was considered statistically significant.

3.7 Sample Size Calculation

As this was an exploratory cross-sectional study in a predominantly unresearched area, sample size calculations were challenging. This study recruited participants via a process of consecutive clinic attendances. It was originally envisaged that in the data collection period over nine months (October 2019-June 2020), all attendees of the Narcolepsy outpatient clinic were eligibility screened. Approximately 15-20 outpatients attend the Narcolepsy outpatient clinic in St. James's Hospital each month. Over a 9-month period, taking the lower threshold of 15 per month, it was estimated that approximately 135 outpatients would be eligibility screened. Allowing for those not meeting the inclusion criteria, repeat visit attenders, and a 10-20% refusal rate, it was originally estimated that 70 people would participate in this study.

3.8 Data Management:

In compliance with GDPR, data was only be shared with those in the project team. Data will be archived for seven years as per the institutional ethical obligations, in a password-protected data drive for purposes including subsequent dissemination in peer-reviewed journals or at national and international conferences. A Data Protection Impact Assessment form was completed and submitted to the Data Impact Officer in Trinity College Dublin. This ensured that the risks associated with processing personal data and the impact on individuals were minimised throughout the research project.

Chapter 4: Results

4.1 Recruitment

In total, 54 people with narcolepsy were screened for eligibility between November 2019 and March 2020. A total of 23 participants completed some or all of the assessment battery. Figure 13 outlines the flow of participants through the study. Due to COVID-19 restrictions, recruitment and testing for this study ceased on March 7th, 2020.

Thirty participants were excluded. Fourteen participants were eligibility screened and had originally consented to participate in the study but were unable to be assessed due to Covid-19 restrictions. The time of assessment was the most common reason for refusing to participate (n=6). One eligible person with vaccine-related narcolepsy declined to participate due to concerns that the assessment may affect a pending legal action.

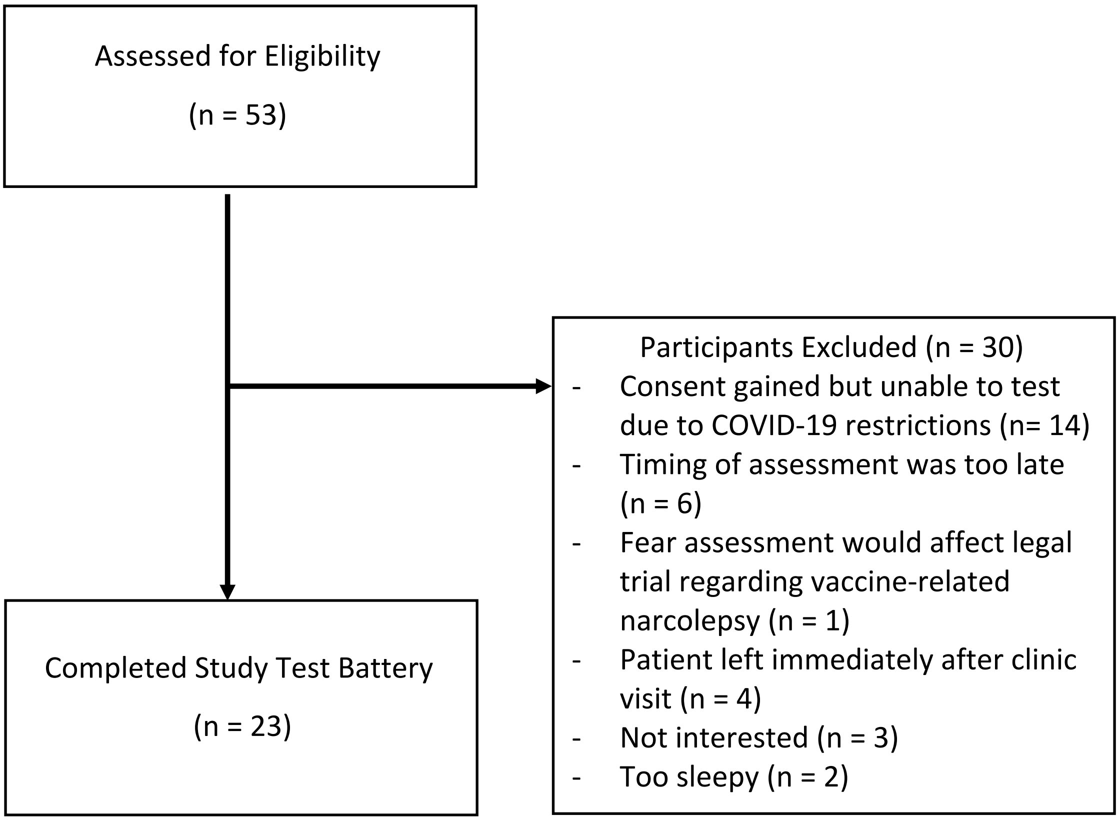


Figure 13: Flow Diagram of Participants through the Study

4.2 Demographic Characteristics

The demographics characteristics of the recruited sample are provided in Table 5 below. Just over half of the sample was female (n=13, 56.52%). Nearly all participants were diagnosed with NC (n=22, 95.65%). The mean age of participants was 31.53 (±13.17) years, with an age range of 20-63 years. The majority of participants lived with their families (n=19, 82.60%).

4.2.1 Education/Employment

Of the recruited participants, 39.13% (n=9) were employed, 3.04% were unemployed (n=3) and 47.83% (n=11) were in full-time education. The highest educational achievement for nearly half of participants was the Leaving Certificate (n=12, 47.83%), whilst 43.48% (n=10) had achieved a Bachelors degree. Additionally, 11 participants (47.83%) were currently enrolled in Third Level education. One participant (4.35%) had obtained a Masters degree.

4.2.2 Body Mass Index (BMI)

A BMI was obtained for all participants, with results summarised in Figure 14. The sample was relatively evenly distributed, with approximately one-third of participants' BMI being classified as normal (n=8, 34.78%), overweight (n=7, 30.43%), and obese (n=8, 34.78%).

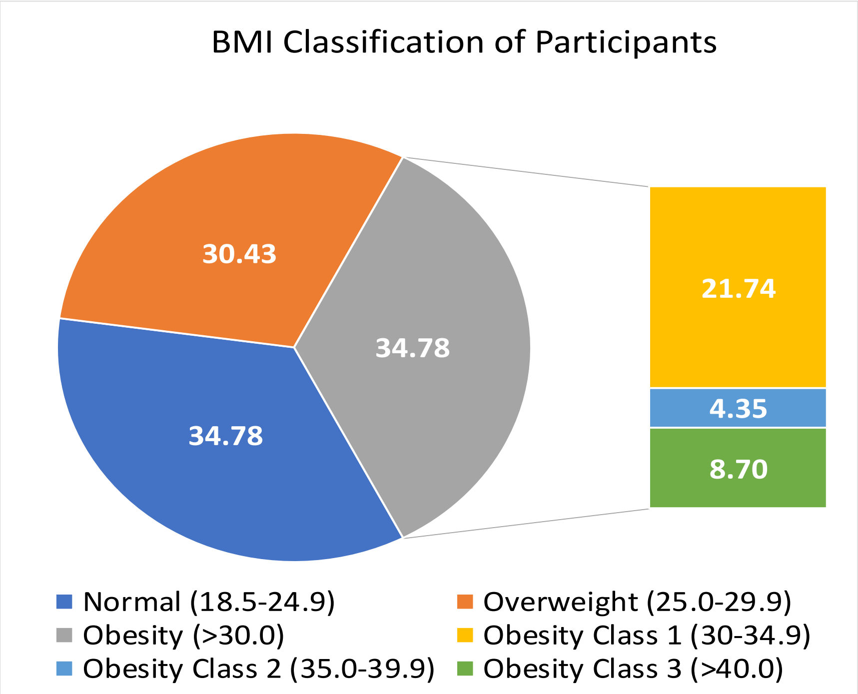


Figure 14: Participants' BMI Classification

Table 5: Demographic Characteristics of Study Participants

	N	%
Gender		
Males	10	43.48
Females	13	56.52
Subtype		
Narcolepsy with Cataplexy	22	95.65
Narcolepsy without Cataplexy	1	4.35
Age		
Age, Years Mean (SD)	31.52 ± 13.17	
Age, Years Range	20 - 63	
Median Age	25	
Living Arrangements		
Alone	2	8.70
Partner	2	8.70
Family	19	82.60
Highest Educational Achievement		
Second Level	12	52.17
Third Level	11	47.83
Current Education/Employment status		
Currently Enrolled as a Student	11	47.83
Employed	9	39.13
Unemployed/Retired	3	3.04
Medications (n = 38)		
Modafinil	13	34.21
Venlafaxine	9	23.68
Wakix	5	13.16
Concerta	4	10.53
Ritalin	4	10.53
Other	3	7.89

4.2.3 Medications

All participants were on at least one prescribed drug to manage their narcolepsy-related symptoms. The number of medications prescribed ranged from 1-3, with a mean of 1.69 ± 0.77 narcolepsy medications prescribed to participants. The most commonly prescribed medication was modafinil, accounting for 34.21% of responses (n=13), followed by Venlafaxine (n=9, 23.68%). The least prescribed medications were Sodium Oxybate (n=2, 5.26%) and Methylphenidate (n=1, 2.63%). The breakdown of medications used by the study sample can be found in Figure 15 below.

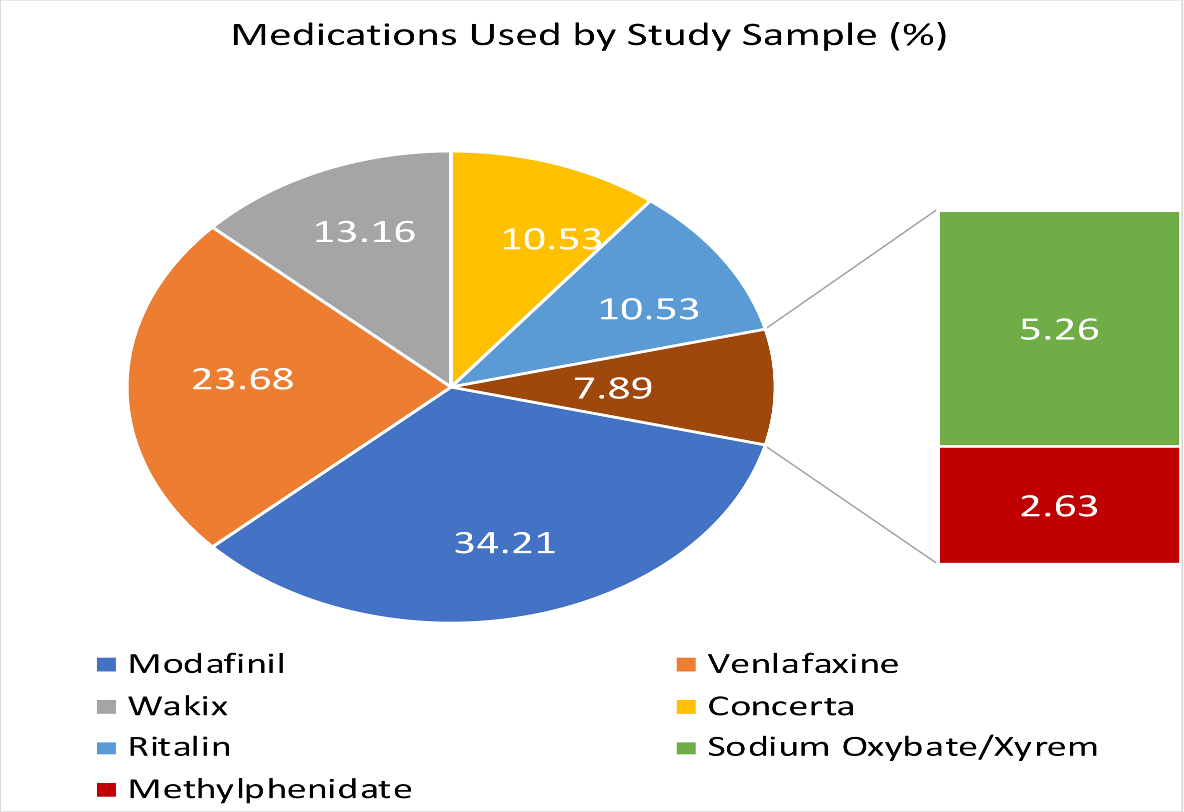


Figure 15: Medications used by Study Sample

4.3 Physical Outcomes

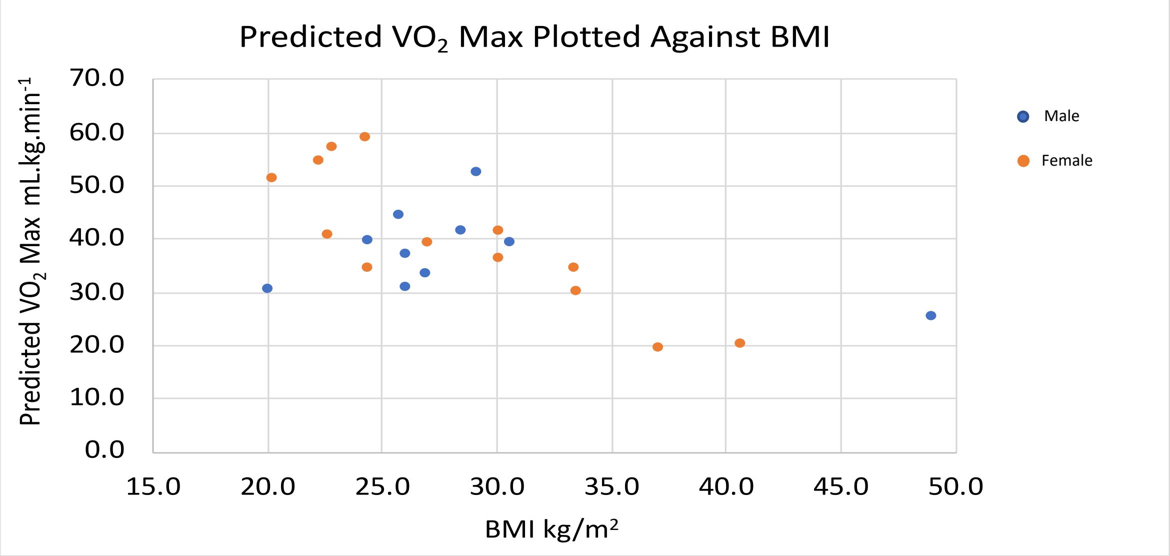
4.3.1 Cardiopulmonary Fitness

All participants completed the YMCA Submaximal Bike test. The collective group median (IQR) predicted VO_2 max for this population was 38.8 (10.8) mL.kg.min^{-1}. The predicted VO_2 Max in males of 39.3 (9.5) mL.kg.min^{-1} was slightly higher than the predicted VO_2 Max observed of 37.4 (16.9) mL.kg.min^{-1} observed in females (Table 6). However, the difference between the predicted VO_2 Max values between male and female participants were found to be insignificant (p = 0.69).

Table 6: Predicted VO_2 Max as Estimated by the YMCA Submaximal Bike Test

Subgroup		Median Predicted VO_2 Max	Interquartile Range
Overall	**(n = 23)**	**39.0**	**10.8**
NC	**(n = 22)**	**38.2**	**11.6**
NwC	**(n = 01)**	**40.6**	**NA**
Males	**(n = 10)**	**39.3**	**9.5**
Females	**(n = 13)**	**37.4**	**16.9**

No significant correlations were identified between participant age ($r_s(21) = -0.334$, p=0.119) and gender ($r_s(21) = 0.087$, p=0.693) and predicted VO_2 max. A significant negative correlation ($r_s(21) = -0.632$, p=0.01) was identified between participant BMI and predicted VO_2 max. A scatter plot is used to illustrate this in Figure 16.



4.3.2 Dynamometry

All participants completed handgrip dynamometry. The median (IQR) grip strength of the sample was 33.6 (7.5) kg. The grip strength of 44.2 (7.1) kg observed in males was higher than the 23.9 (3.7) kg observed in females (Table 7).

Table 7: Mean Grip Strength (Kg) of Study Sample

Subgroup		**Median Grip Strength (Kg)**	**Interquartile Range**
Overall	**(n = 23)**	**33.6**	**17.5**
NC	**(n = 22)**	**35.1**	**18.4**
NwC	**(n = 01)**	**22.1**	**NA**
Males	**(n = 10)**	**44.2**	**7.1**
Females	**(n = 13)**	**23.9**	**3.7**

The handgrip strength observed in both the male and female groups were averaged and compared to the age and gender-matched norms obtained from a study by Steiber (2016), as shown in Figure 17 below. Significant differences were observed between male participants and their age-and-gender matched comparators (p=0.05), whereas no significant differences were observed between female participants and normative values (p=0.12).No significant correlations were identified between total grip strength and participant age ($r_s(21) = -0.387$, p=0.068, $r_s(21) = -0.41$, p=0.052) and BMI ($r_s(21) = -0.1$, p=0.65, $r_s(21) = -0.085$, p=0.7).

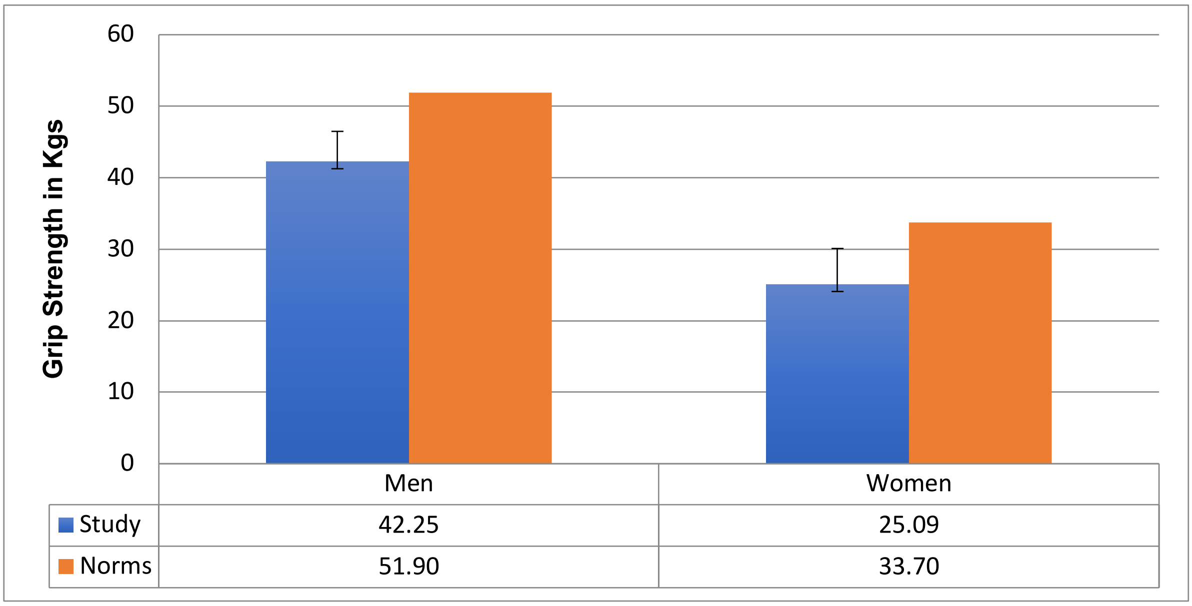


Figure 17: Bar Chart of Recorded Grip Strength Compared to Normative Values

4.3.3 Countermovement Jump Test

All participants completed the Countermovement Jump test. The median (IQR) peak power/body mass (W/Kg) of the sample was 41.8 (10.6) W/kg. The peak power/body mass of 43.2 (20.3) W/kg observed in males was slightly higher than the 41.4 (6.6) W/kg observed in females (Table 8). No statistically significant differences were observed between male and female participants (P=0.2).

Table 8: CMJ Performance of Study Sample

Subgroup		Median Peak Power/Body Mass	Interquartile Range
Overall	**(n = 23)**	**41.8**	**10.6**
NC	**(n = 22)**	**41.5**	**11.7**
NwC	**(n = 01)**	**41.9**	**NA**
Males	**(n = 10)**	**43.2**	**20.3**
Females	**(n = 13)**	**41.4**	**6.6**

The peak power/body mass observed in both the male and female groups was shown compared to the age and gender-matched norms obtained from a study by Tsubaki et al. (2009) in Figure 18. No significant differences were observed between age-and-gender-matched normative values and male participants (p=0.18) and female participants (p=0.67), respectively. No significant correlations were identified between peak power/body mass and participant age ($r_s(21) = -0.074$, p=0.737), and BMI ($r_s(21) = 0.005$, p=0.981).

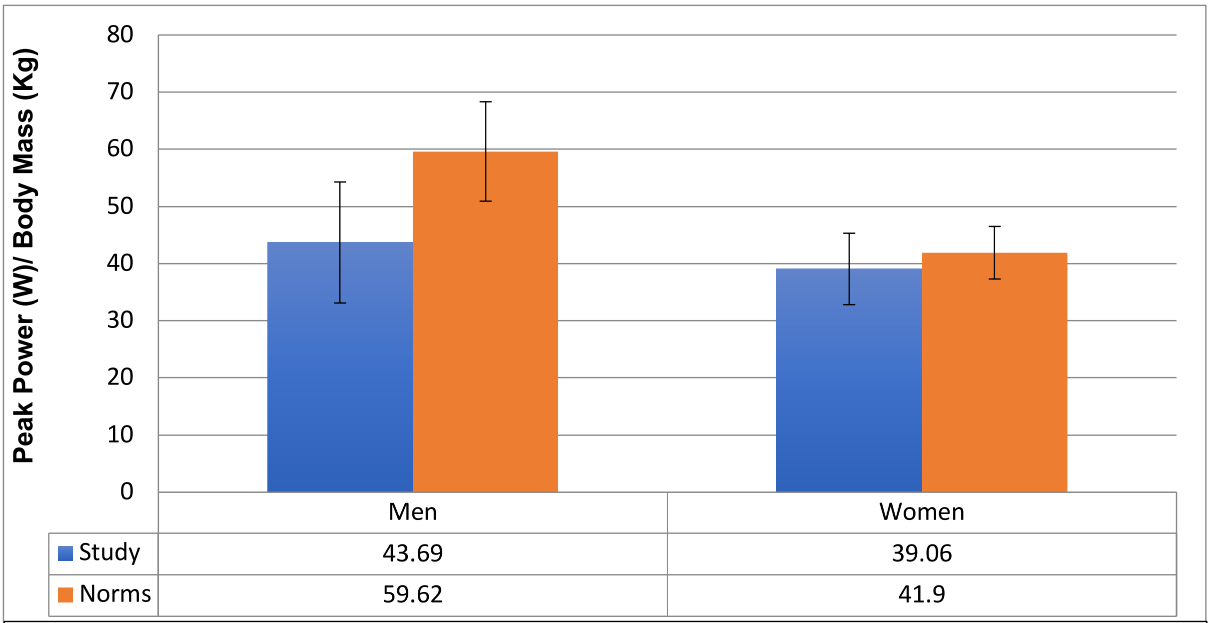


Figure 18: Bar Chart of CMJ Compared to Normative Values

4.3.4 ACSM Push Up Test

All participants completed the ACSM Push Up test. The median (IQR) number of push-ups performed by the participants was 10.0 (10.0) repetitions, and the number of push-ups completed ranged from 1 to 32. The number of repetitions performed by males (10.0 (9.3)), was higher than that observed in females (8.0 (9.0)). Statistically insignificant between-group differences were observed between the male and female participants (p=0.13)

Table 9: ACSM Press Up Performance

Subgroup		Median Performance	Interquartile Range
Overall	**(n = 23)**	**10.0**	**10.0**
NC	**(n = 22)**	**9.5**	**10.5**
NwC	**(n = 01)**	**10.0**	**NA**
Males	**(n = 10)**	**10.0**	**9.3**
Females	**(n = 13)**	**8.0**	**9.0**

No significant correlations were identified between participant BMI on their push up test performance ($r_s(21) = -0.342$, p=0.111). However, a significant negative correlation was identified between participant age and push up performance ($r_s(21) = -0.458$, p=0.05), with performance decreasing with age. A scatter plot of push up performance compared to age illustrates this finding. below (Figure 19).

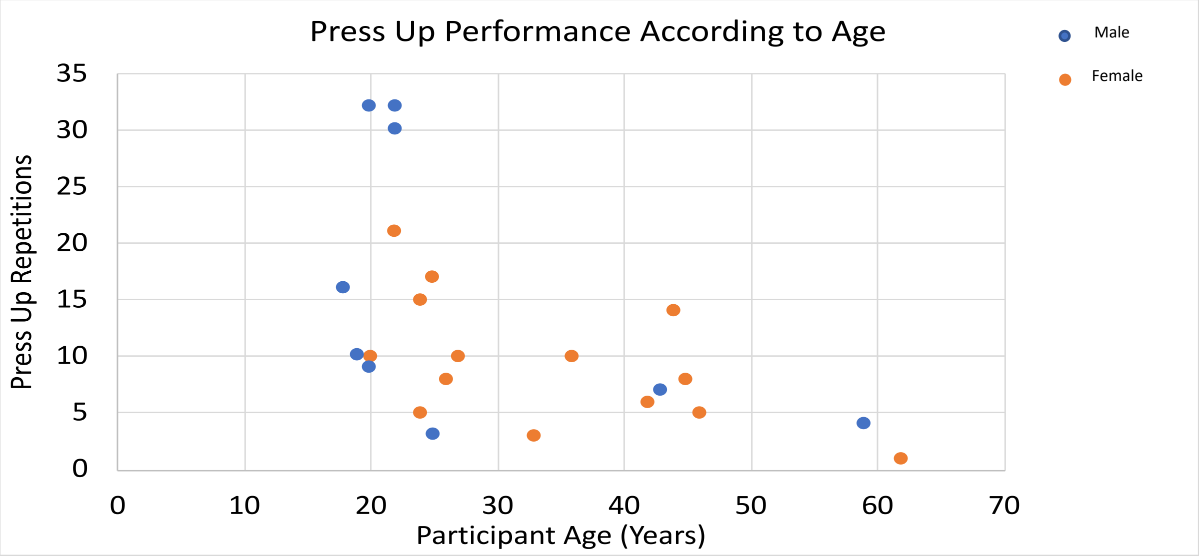


Figure 19: Scatter Plot of Press Up Repetitions Compared to Participant Age

4.3.5 Wall Squat Test

All participants completed the Wall Squat Test. The median (IQR) duration of the participant's performance was 44.9 (36.3) seconds, with a range of 9.84 to 122.00 seconds. The median duration observed in males was 52.0 (30.2) seconds, and 36.3 (39.2) seconds in females (Table 10). Statistically insignificant between-group differences were observed between the male and female participants (p=0.43).

Table 10: Wall Squat Duration of Study Sample

Subgroup		**Median Performance (S)**	**Interquartile Range**
Overall	**(n = 23)**	**44.9**	**36.3**
NC	**(n = 22)**	**41.0**	**41.4**
NwC	**(n = 01)**	**48.3**	**NA**
Males	**(n = 10)**	**52.0**	**30.2**
Females	**(n = 13)**	**36.3**	**39.2**

There was no significant correlation between participant age on wall squat performance ($r_s(21) = -0.269$, p=0.215). However, a significant negative correlation was identified between participant BMI and wall squat performance ($r_s(21) = -0.632$, p=0.01). A scatter plot of wall squat duration compared to BMI illustrates this finding below (Figure 20).

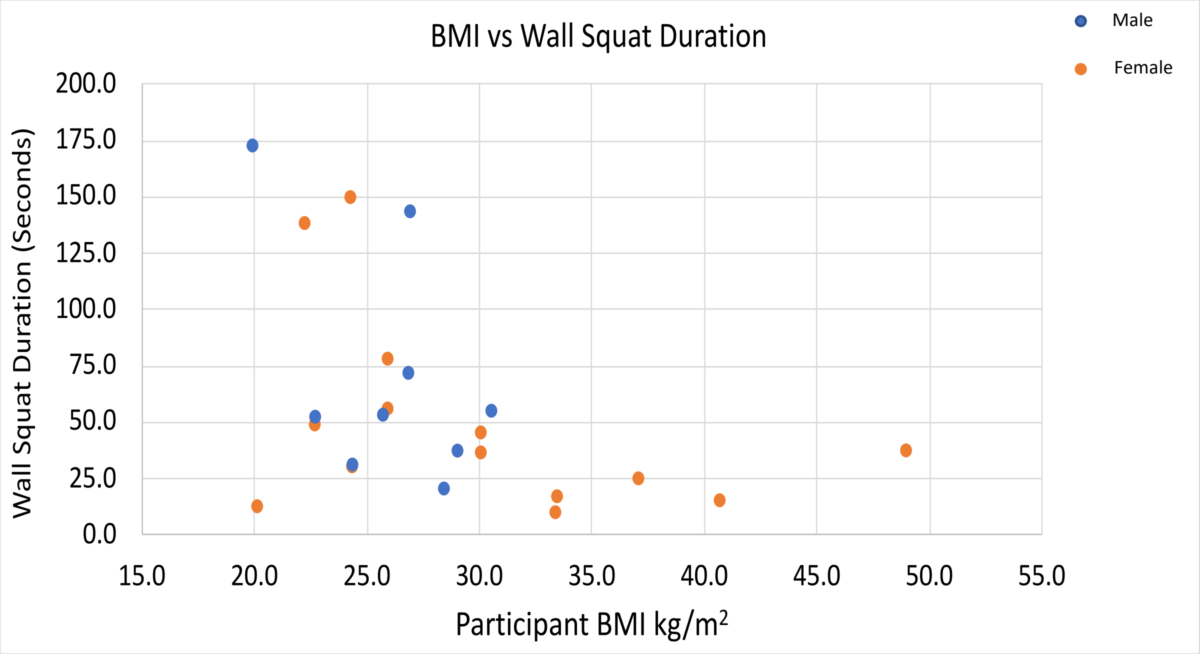


Figure 20: Scatter Plot of Wall Squat Duration Compared to Participant BMI

4.3.6 Actigraphy

A total of 13 participants completed the Actigraphy component of the test battery, resulting in an adherence rate of 54.17% for this measure. This level of low completion for actigraphy may be attributed to a combination of equipment shortages and Covid-19 precautions considerably reducing the opportunities to gather this actigraph data from participants. Additionally, actigraphy was the only outcome measure that could not be completed on the same day as the other measures which may have contributed to the low compliance observed.

The median (IQR) daily amount of moderate-vigorous physical activity (MVPA) performed was 37.1 (31.2) minutes as measured by actigraphy. The amount of MVPA performed in males (46.7 (32.9) minutes) was higher than that observed in female participants (37.3 (31.2) minutes) (Table 11). The median (IQR) daily duration spent sedentary by participants over the measurement period was 9.1 (11.7) hours, with prolonged bouts sedentary behaviour ranging from 10 minutes to 22.8 hours. The mean length of a sedentary bout was 35.95 (± 18.83) minutes. The levels of sedentary behaviour observed in female participants (15.0 (8.6) hours) was considerably higher than that observed in male participants (3.6 (7.1) hours) (Table 11).

The Mann-Whitney U test was used to explore the influence of participant gender on physical activity and sedentary behaviour. From the data gathered, it can be concluded that the mean duration of sedentary bouts in the female group was statistically significantly higher than the male group (*U* = 5.00, *p* = 0.041).

Table 11: Daily MVPA and Sedentary Behaviour as measured by Actigraphy

Subgroup		MVPA (mins)	Interquartile Range	Sedentary Behaviour (hours)	Interquartile Range
Overall	**(n = 13)**	**37.3**	**31.2**	**9.1**	**11.7**
NC	**(n = 12)**	**37.0**	**30.4**	**11.4**	**11.9**
NwC	**(n = 01)**	**67.8**	**NA**	**3.5**	**NA**
Males	**(n = 06)**	**46.8**	**32.9**	**3.6**	**7.1**
Females	**(n = 07)**	**37.3**	**17.3**	**15.0**	**8.6**

Activity intensity

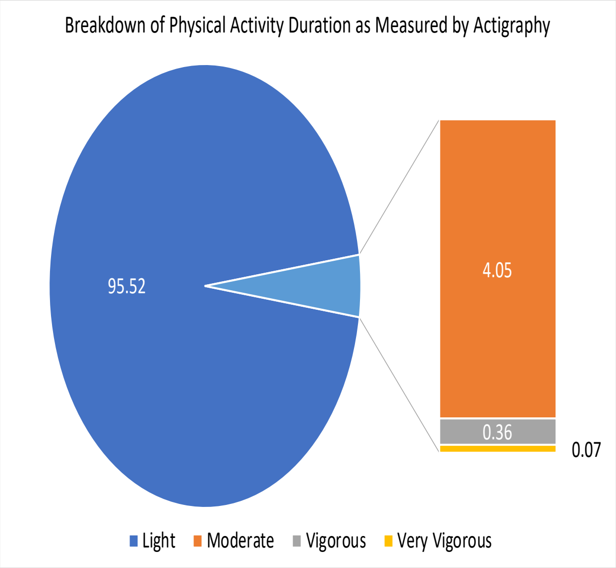


Figure 21: Breakdown of Physical Activity as Measured by Actigraphy

The mean Kilocalories expended through physical activity per day was 263.19 (± 181.13) Kilocalories. Light physical activity was the most common intensity of physical activity and accounted for 95.52% of completed activity. The remainder of moderate, vigorous and very vigorous activity accounted for 4.48% of physical activity. Very vigorous activity was the least common intensity of physical activity and was completed for a mean of 8.61 (± 15.06) minutes over the measurement period and accounting for 0.07% of all completed activity.

4.4 Quality of Life

4.4.1 SF36

The pooled mean results of the SF36 domains are reported with 95% confidence intervals in Table 12. From the obtained results, the mental component summary scores (38.13 ± 11.20) were lower than the physical component summary scores (46.32 ± 8.44). The most affected domains of the SF36 were Vitality (37.04 ± 22.53), Physical Role Limitations (55.30 ± 25.50) and perceived General Health (55.30 ± 25.50). The least affected domains were Physical Functioning (76.74 ± 17.81), and Pain (73.39 ± 26.56) (Table 12).

General correlations between participant demographic characteristics and SF36 results are provided below in Table 12. A significant negative correlation was found between gender and Bodily Pain in males ($r_s(21) = -0.358$, $p=0.01$). Additionally, a negative correlation was found between lower BMIs and General Health ($r_s(21) = -0.457$, $p=0.05$). No other significant correlations were found between BMI, gender and age and SF36 scores. Females reported poorer quality of life overall than males, with the greatest differences being observed in the Bodily Pain, Vitality and Emotional Role Limitations domains. However, no statistically significant differences were identified between males and females in the physical (p=0.410) and mental (p=0.738) component summaries.

Table 12: Pooled Mean SF36 Results and Correlators

	PF	**RP**	**BP**	**GH**	**PCS**	**V**	**SF**	**RE**	**MH**	**MCS**
Pooled Mean	76.74	44.57	73.39	55.30	46.32	37.04	59.80	53.94	66.00	38.13
Standard Deviation	17.81	38.40	26.56	25.50	8.44	22.53	27.19	42.46	17.59	11.20
Males	82.00	50.00	85.00	56.00	48.14	47.00	65.00	60.00	71.60	41.45
Standard Deviation	17.83	39.09	17.72	25.91	7.39	17.19	21.08	46.62	15.83	10.67
Females	72.69	40.38	64.46	54.77	44.92	29.38	55.81	49.28	61.69	35.58
Standard Deviation	17.39	38.92	29.31	26.23	9.22	23.72	31.34	40.27	18.25	11.33
Correlators										
Age	-0.290	-0.097	-0.300	-0.021	-0.178	-0.198	-0.176	-0.311	-0.151	-0.220
Gender	0.326	0.963	**-0.358****	-0.060	-0.195	-0.297	-0.089	0.706	-0.204	-0.100
BMI	-0.243	-0.15	0.025	**-0.457***	-0.282	-0.246	-0.397	-0.238	-0.121	-0.249
*= Correlation significant at p=0.05 **= Correlation significant at p=0.01										

4.4.2 FOSQ

The pooled mean scores for the FOSQ domains and standard deviations are reported in Table 13. From the results obtained, vigilance (48.50 ± 15.67) and Activity Levels (54.72 ± 15.49) were identified as the most affected domains of health-related quality of life. The Intimacy/Sexuality (58.26 ±23.48) and Social Outcomes (59.57 ± 21.21) domains were the least affected FOSQ domains.

General correlations between participant demographic characteristics and FOSQ results (Table 13). A significant correlation was identified between gender and the Intimacy/Sexual domain (r_s(21) = -0.467, p=0.05), and Total FOSQ scores (r_s(21) -0.465, p=0.05) in males. No other significant correlations were identified between age, gender and BMI and FOSQ scores (Table 13). Poorer quality of life was reported overall by females, with Intimacy/Sexuality, Activity Levels and Social Outcomes being the most affected domains. No statistically significant differences were found between male and female participants in all FOSQ subscales and total FOSQ scores.

Table 13: Pooled Mean FOSQ Results and Correlators

	General Productivity	**Social Outcome**	**Activity Levels**	**Vigilance**	**Intimacy/ Sexual**	**Total Score**
Pooled Mean	57.37	59.57	54.72	48.50	58.26	68.83
Standard Deviation	14.29	21.21	15.49	15.67	23.48	17.80
Males	60.75	63.00	58.33	50.07	62.00	73.54
Standard Deviation	14.46	18.89	13.10	16.46	22.01	19.95
Females	54.76	56.92	51.94	47.29	55.38	65.21
Standard Deviation	14.17	23.23	17.09	15.60	25.04	15.80
Correlators						
Age	-0.134	-0.103	-0.183	-0.106	-0.028	-0.169
Gender	-0.355	-0.269	-0.159	-0.342	**-0.467***	**-0.465***
BMI	0.04	0.051	0.056	0.129	-0.05	0.015
*= Correlation significant at p=0.05 **= Correlation significant at p=0.01						

4.5 Symptom Severity

All participants completed the Epworth Sleepiness Scale. Scores were summated, and the total score obtained was found to be 64.86 ±19.09. The activities which were most likely to lead to sleeping were lying down (92.75 ± 17.28) and being a passenger in a car (86.96 ± 24.08). The activities least likely to lead to sleeping were sitting and talking (30.43 ± 31.64) and sitting in traffic whilst driving (28.99 ± 19.00). The scores for each activity of the ESS are outlined below in Figure 22.

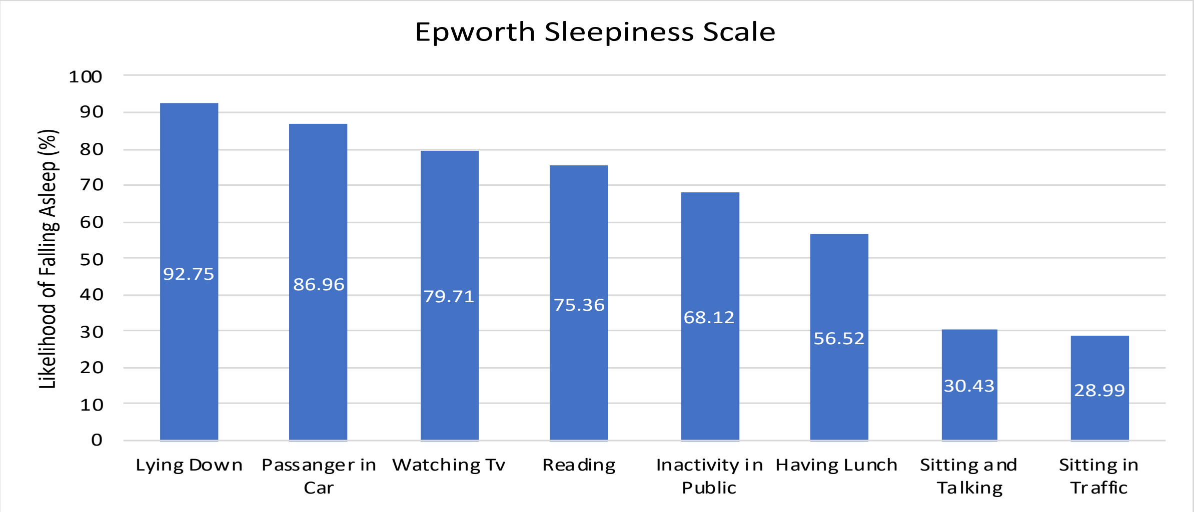


Figure 22: Activities Likely to Cause Sleep as Measured by the Epworth Sleepiness Scale

A significant positive correlation was identified between total ESS scores and age, with sleepiness severity increasing with participant age ($r_s(21) = 0.437$, p=0.05). The ESS scores for participants were plotted against age and gender in Figure 23. No significant correlation was identified between total ESS scores and participant BMI ($r_s(21) = -0.148$, p=0.499), or between males and females (p=0.203).

Figure 23: Scatter Plot of Epworth Scores Compared to Participant Age

Narcolepsy Severity Scale

All 23 participants completed the Narcolepsy Severity scale. Sleep attacks were identified as the most severe symptom of narcolepsy (60.52 ± 22.41), followed closely by cataplexy (59.20 ± 30.72). Sleep paralysis (50.99 ± 22.56), and hallucinations (51.63 ± 25.37) were found to be the least severe symptoms (Figure 24). Sleep attacks were the most frequently experienced symptom, occurring daily for 56.5% of respondents (n=13). General and Partial Cataplexy were both experienced daily in 21.7% of participants (n=5). Sleep paralysis and hallucinations were the least frequently occurring symptoms, both occurring in only 13% of respondents daily, respectively. The frequency of these symptoms is outlined in Figure 24.

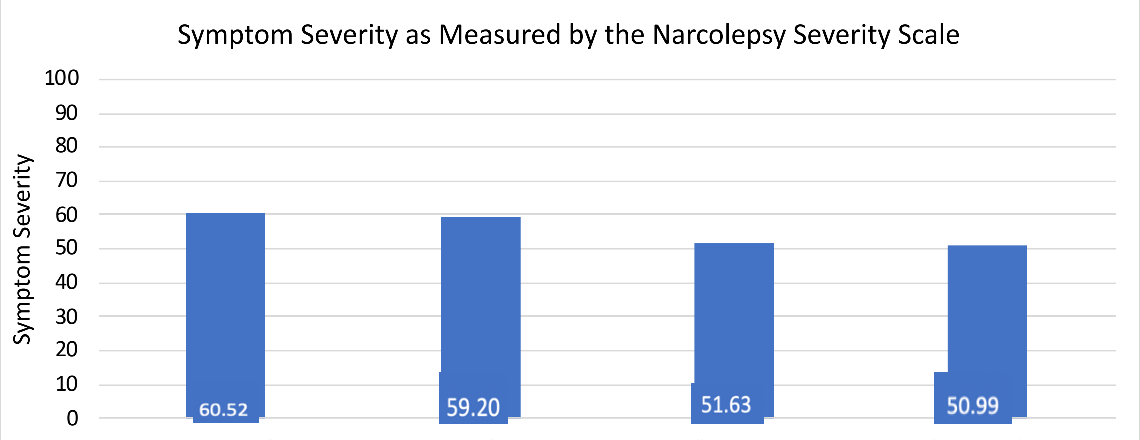


Figure 24: Bar Chart of Symptom Severity as Measured by the Narcolepsy Severity Scale

Approximately one-third reported experiencing sleep attacks on a weekly basis (30.4%, n=7), whilst over half of the respondents (n=13, 56.5%) reported more than one sleep attack per day (Figure 25). The interim period between sleep attacks was generally ranged between 1-3 hours (n=7, 30.4%) and 3-6 hours (n= 5, 21.7%). Respondents were divided regarding how they felt following a sleep attack, with 47.83% (n=11) reporting they feel refreshed, and 52.17% (n=12) reporting they feel very tired after an attack. The majority of respondents (n=19, 82.6%) reported that their sleep attacks were affecting their personal and professional lives. Of the respondents who could drive (n=14), 57.14% reported that sleep attacks affected their ability to drive.

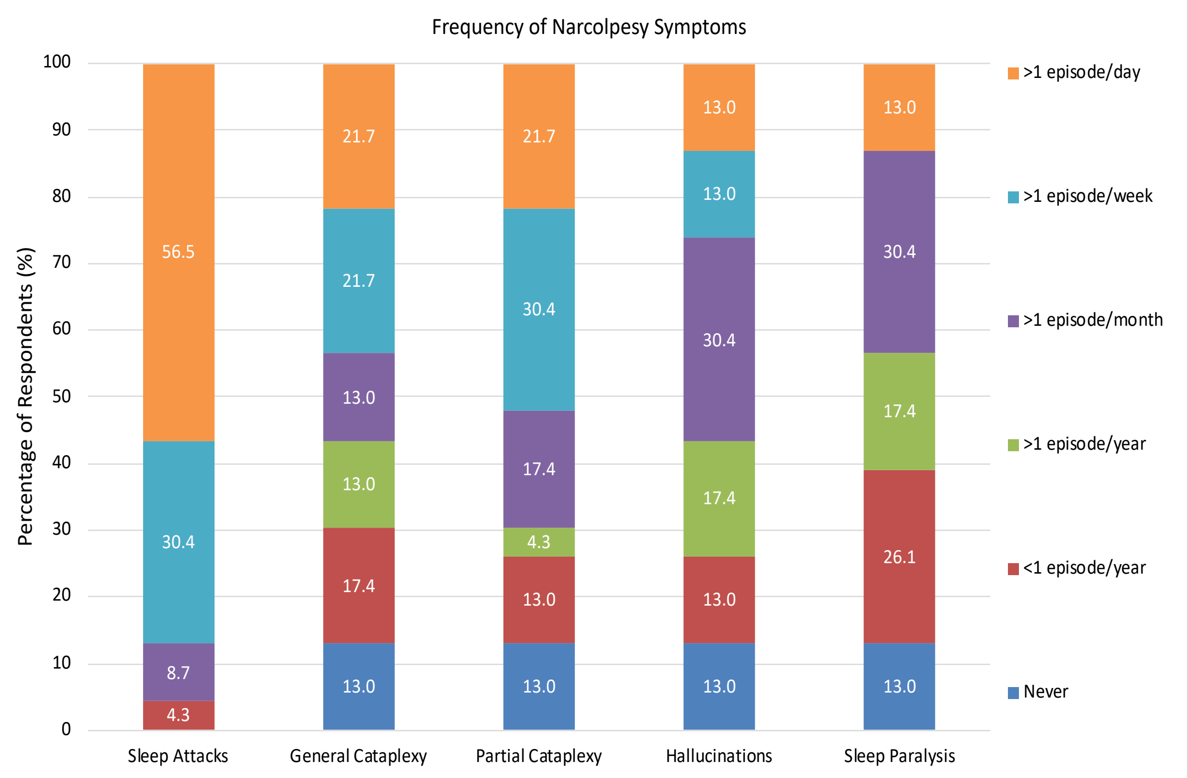


Figure 25: Bar Chart of the Frequency of Narcolepsy Symptoms

The majority of respondents (87.0%) reported that they had experienced cataplexy. The frequency of generalized cataplexy attacks ranged from less than one episode per year (13%) to more than one episode per day (21.7%). Similarly, of the 87% of respondents reported experiencing partial cataplexy attacks, 52.1% reported experiencing attacks every week. Over half of participants (57.89%) reported that cataplexy affected their work, social or family life.

The majority of respondents (n=20, 87%) reported having experienced hallucinations. The frequency of hallucinations varied with 30% (n=6) experiencing hallucinations weekly, and 35% experiencing them on a monthly, and annual basis, respectively. Over half (60%) of the participants reported that their hallucinations do not bother them, whilst 20% of the participants reported that they are very bothered by their hallucinations. Similarly, 87% of respondents reported experiencing sleep paralysis when falling asleep or waking up. Sleep paralysis frequency varied, with 15% of respondents experiencing daily episodes (n=3), 35% experiencing monthly episodes (n=7), and 50% (n=10) experiencing annual episodes of sleep paralysis. Over half (60%) of the participants reported that their sleep paralysis does not bother them, whilst 25% of respondents found their sleep paralysis very bothering.

4.6 Self-Reported Sedentary Behaviour and Physical Activity

All participants completed both the Physical Activity Vital Sign Questionnaire and the Sedentary Behaviour Questionnaire. The average total duration spent on sedentary activities was 1225 ± 95.92 minutes per day. The most time devoted to a sedentary task was work, which was performed on average for 310 minutes daily. Other notable sedentary activities included watching television, which was performed for 270 minutes daily, and transport which was performed for 210 minutes daily. Exercise was the least performed activity, being performed for a mean of 40 (± 27.14) minutes daily. However, the median aerobic exercise duration was found to be 30 minutes per day. The average duration of daily activities is outlined below in Figure 26.

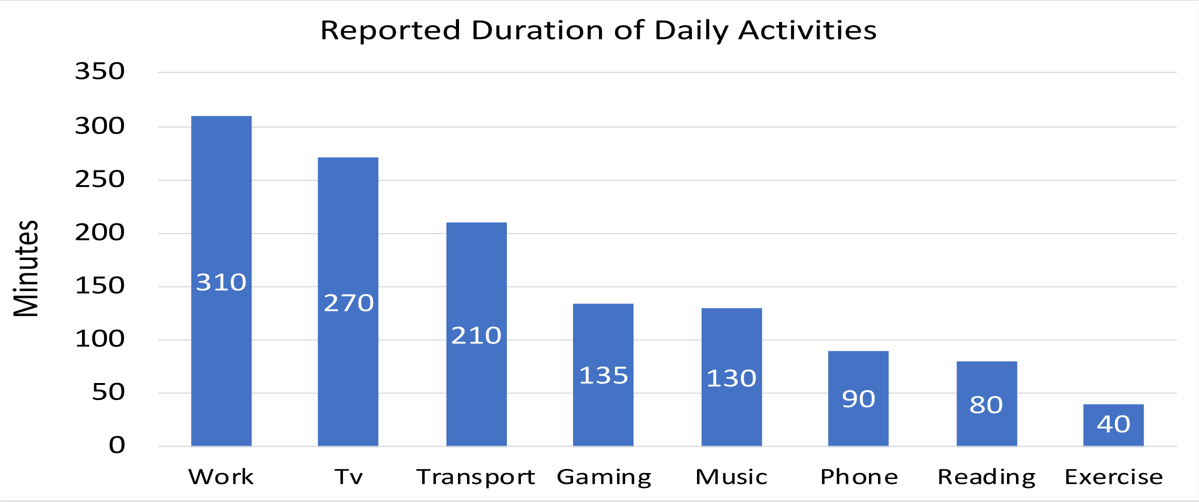


Figure 26: Bar Chart of Reported Durations of Daily Activities

The breakdown of the duration spent on each activity is outlined in Figure 27. The activities that witnessed the longest duration of sedentary bouts were work and listening to music, both of which had participants perform these tasks for more than 6 hours. Other notable activities included watching television, gaming, and listening to music which were performed for 4-5 hours, respectively. The most frequently reported duration of sedentary bouts was 15-30 minutes.

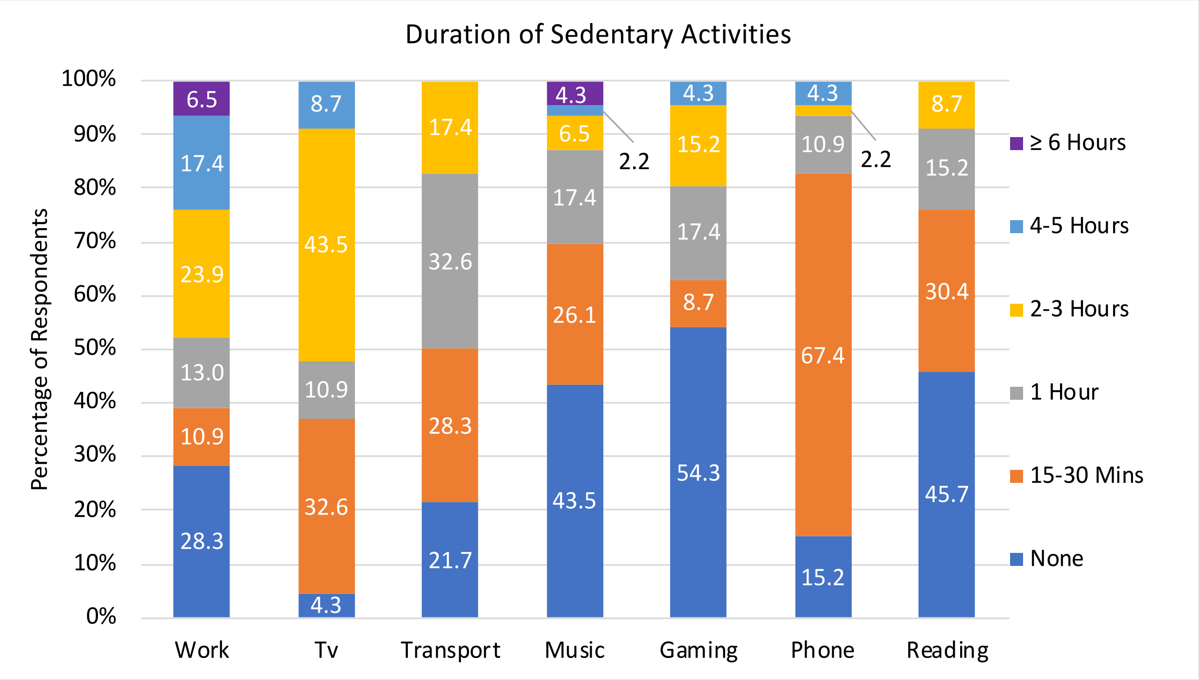


Figure 27: Breakdown of the Duration that Sedentary Activities were Performed

Aerobic exercise was performed on 3.91 ± 2.04 days per week, for an average duration of 37.87 ± 27.14 minutes per session. The sessions ranged from 0-120 minutes in length, with a median of 30 minutes, respectively. The average weekly duration of aerobic exercise was 175 ± 164.13 minutes per week, with a median of 150 minutes and mode of 180 minutes weekly. The durations of aerobic exercise were plotted against participant age and gender in Figure 28.

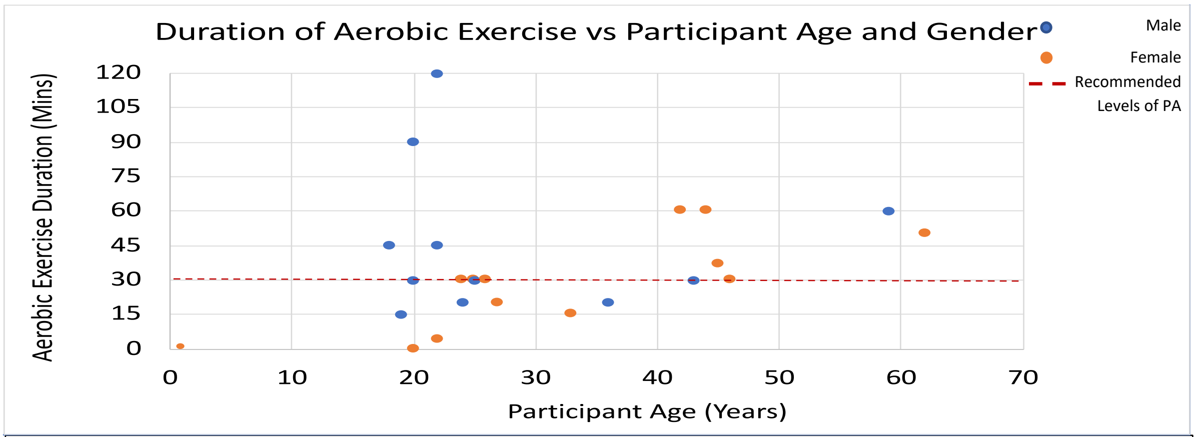


Figure 28: Duration of Aerobic Exercise Compared to Participant Age

4.7 Thematic Analysis of Open-Ended Responses

All participants (n=23, 100%) answered the open-ended questions, and six main themes were identified from their responses. Data analysis was guided by the Braun and Clarke (2006) six-phase framework. The six main themes were: Barriers to Exercise, Motivators, Social Concerns, Health Concerns, Awareness of Abilities and Suggestions for the Role of Physiotherapy (Table 14).

Table 14: Overview of Main Themes

Theme	Subthemes
1. Barriers to Exercise	• Psychological Barriers Limiting Participation in Exercise • Fatigue and Tiredness Limiting Ability to Exercise • Fear of Cataplexy Limiting Participation in Exercise • Accessibility Limiting Participation in Exercise
2. Motivators	• Career/Education • Social Wellbeing • Health and Wellbeing
3. Social Concerns	• Impact of Narcolepsy on Career and Education • Impact of Narcolepsy Familial Relationships • Impact of Narcolepsy on Social Life
4. Health Concerns	• Weight Gain Following Diagnosis • Reduction of Physical Activity • Pain
5. Awareness of Abilities	• Decline of Physical Performance • Difficulty of Test Battery
6. Suggestions for the Role of Physiotherapy	• Physiotherapist Prescribed Exercise Programmes • Advice on Reintroducing Exercise • External Source of Motivation to Promote Adherence

Theme 1: Barriers to Exercise

Nearly all participants (n=22, 95.65%) reported exercising on a weekly basis. Respondents were asked what the main barriers they encounter that prevent them from exercising. From the responses obtained from participants, five main barriers were identified.

i. Psychological Barriers Limiting Participation in Exercise

Participants expressed several psychological barriers towards exercising. For some participants, their anxiety towards exercising prevented them from participating in regular activity.

> *"My anxiety - getting out can be quite difficult."* | **N07 (F, 45)**

For others, their low mood posed a considerable barrier towards regularly engaging in exercise.

> *"My mood can be quite low, or apathetic. I feel this has been a major barrier to exercising, like I can do it, but I couldn't care to do it."*| **N04 (F, 24)**

Other participants expressed that their lack of confidence made them reluctant to exercise.

> *"if I feel like I don't know what I'm doing, and people are staring at me it can really put you off going."* | **N08 (F, 26)**

ii. Fatigue and Tiredness Limiting Ability to Exercise

Fatigue and tiredness, secondary to narcolepsy, were frequently reported by participants as considerable barriers towards exercise. One participant described their difficulties with managing a finite amount of energy.

> *"At the end of the day, I just want to go to bed instead of going for a run/going to the gym."* | **N01 (F, 25)**

Another participant described the stigma surrounding narcolepsy and experiencing fatigue as a young adult.

> "I hate using this excuse, but I just feel tired." | **N04 (F, 24)**

Disrupted night-time sleeping was also reported to contribute to fatigue and tiredness and presented a considerable barrier to engaging in exercise.

> *"It's very difficult to exercise when sleepy. I like to exercise in the morning but am unable to when I sleep poorly."* | **N06 (F, 42)**

iii. Fear of Cataplexy Limiting Participation in Exercise

With 95.65% of participants (n=22) having type 1 narcolepsy, cataplexy was a frequently reported barrier towards exercising in this sample. Several respondents reported having prior experiences with cataplexy that have discouraged them from exercising.

> *"I'm scared to do things because of my cataplexy. I had one bad attack in a gym before, and that's made me more anxious overall."* | **N04 (F, 24)**

Another participant expressed that her self-consciousness with exercise exacerbated her cataplexy

> *"Feeling weak, anxious or self-conscious, particularly in a gym, can greatly increase my likelihood of experiencing cataplexy."* | **N08 (F, 26)**

Some participants expressed that their cataplexy prevented them from participating in previously enjoyed hobbies.

> *"I used to love playing football when I was younger. I get cataplexy attacks when I'm surprised or excited. If running to catch a bus is enough to trigger it, I think exercise would do the same."* **N09 (M, 59)**

It must be noted that no adverse incidents relating to cataplexy occurred throughout the testing process.

iv. Accessibility

Accessibility-related issues were the final barrier towards exercising reported by this sample. Some participants expressed that timing was an issue.

> *"Time constraints, making time to do things can be difficult. I have access to a gym but I use it sparingly"* | **N20 (M, 19)**

For others, the financial costs associated with exercising prevented them from exercising.

> *"I used to exercise in a gym for 40 mins, but the price is too high."* | **N16 (F, 63)**

The last major accessibility-related barrier reported by participants related to poor weather conditions, particularly in winter.

> *"The cold weather really discourages me, especially when it is dark."* **N23 (F, 20).**

Theme 2: Motivators

Participants expressed several factors that motivated them to exercise and be active. These motivators ranged from their career/education, prevention of the progression of their condition, their health, and their physical and social wellbeing.

i. Career/Education

The vast majority of the younger participants reported that advancing their career and their education mattered to them the most at this stage in their lives.

> "I'm not letting narcolepsy stop me from pursuing my career" | **N01 (F, 24)**

Some expressed that, to them, exercise and their physical wellbeing were integral to achieving this.

> *"My fitness matters a lot to me, also my family and education - keeping on top of everything at the moment really."* | **N13 (F, 24)**

One participant expressed how she changed her career to something that was more active to help manage her physical wellbeing.

> *"My health and my career are my priorities. I wanted to do something that benefited my health, and that's why I changed careers."* | **N08 (F, 26)**

ii. Social Wellbeing

Maintaining interpersonal relationships was one of the most frequently reported priorities expressed by participants.

> "Staying on top of my work and finding time to socialise and exercise." | **N12 (F, 22)**

Several participants expressed their motivation for improving their physical wellbeing was to ensure that they could spend time with their loved ones.

> *"My family - I want to be able to do stuff with my children"* | **N07 (F, 45)**

Additionally, maintaining balance and control over their lives was a common sentiment expressed by several participants.

> *"I want to keep a healthy balance with everything; my family, my social life, my hobbies and exercise, and my relationships."* | **N11 (M, 22)**

iii. Health and Wellbeing

Maintaining their overall health and wellbeing was a major priority and motivator that was reported by participants in this sample.

> *"I want to lose weight, be happier and improve my life in order to have the energy to do what I want."* | **N04 (F, 24)**

One participant also shared this sentiment of losing weight to improve their overall physical wellbeing.

> "My health is my biggest priority… I need to get back to a normal weight". | **N18 (M, 25)**

Another participant expressed concern regarding the progression of their narcolepsy-related symptoms.

> "Not letting my symptoms get any worse, I can just about handle how it is at the moment." | **N03 (M20)**

Theme 3: Social Concerns

The impact of narcolepsy on social wellbeing was frequently reported by people with narcolepsy in this sample. These social concerns ranged from the impact of narcolepsy on their career, family and relationships, and social life.

i. Impact on Career and Education

Given the young age of the sample, participants were focused on developing their careers.

> *"Getting a job - I'm focused on developing my career at the moment."* | **N17 (M, 22)**

Several participants expressed concern about how narcolepsy would affect their careers. Sometimes, the pursuit of developing their career was prioritised ahead of their health.

> *"My career, I'm not really focusing on my health at the moment. I would like to increase this focus going forwards".* | **N15 (M, 20)**

Other participants were worried about the impact of narcolepsy-related symptoms as they get older.

> "I'm worried if I'll still be able to do what others are able to do in 10 years' time when my youthful energy fades." | **N01 (F, 25)**

ii. Impact on Familial Relationships

Participants expressed the considerable impact narcolepsy can have on their relationships with their families. A father of a young child expressed how his sleepiness was affecting their relationship.

> *"My son, it's difficult falling asleep when I'm spending time with him."* | **N22 (M, 27)**

This sentiment of trying to spend quality time with their children was also shared by another parent.

> *"I want to be able to do stuff with my children, I need to work around everything with my narcolepsy"* | **N07 (F, 45)**

One participant, who was diagnosed with narcolepsy over 30 years ago, expressed how his difficulties with being a parent that has narcolepsy increased with age.

> *"It's not as easy as it used to be, my children are getting older. Life doesn't get easier with age; I feel time is slipping away."* **N09 (M, 59)**

iii. *Impact on Social Wellbeing*

Difficulty with managing their social wellbeing was frequently reported by participants. Participants expressed that keeping their commitments to friends, family, hobbies and education or employment was very important to them.

> *"I want to keep a healthy balance with everything; my family, my social life, my hobbies and exercise, and my relationships. It can be difficult to manage due to narcolepsy but I'll try my best anyways."* | **N11 (M, 22)**

One participant reported the difficulties of maintaining a healthy social life when living with narcolepsy.

> "It feels like you have to work so much harder than others. You only have a limited amount of energy, so oftentimes I have to choose between socialising or studying." | **N01 (F, 25)**

Participants reported having to sacrifice aspects of their lives to prioritise other commitments.

> *"Staying on top of my work and housework, finding time to socialise and exercise. I feel exercise was more important to me previously, but I changed jobs recently and have been finding it difficult."* **N12 (F, 22)**

Theme 4: Health Concerns

Four main health concerns were identified from the open-ended responses. These concerns related to weight gain, pain, and reduced physical activity.

i. Weight Gain

Several participants reported that their weight was the biggest concern regarding their health.

> *"My weight, definitely, I try not to worry about it, but it is an issue."* | **N05 (F, 46)**

Considerable weight gain following receiving a diagnosis of narcolepsy was expressed by several participants. One participant reported great difficulty losing this added weight.

> *" I gained 5 stone after I was diagnosed with narcolepsy 19 years ago, and I've been fighting to lose it ever since."* | **N16 (F, 63)**

The deleterious effects of this weight gain are not only physical but can also impact mental wellbeing.

> "I have put on 10 stone since I've been diagnosed. I don't like the way I look; I am self-conscious about my weight, particularly when playing live music." | **N18 (M, 25)**

ii. Reduced Physical Activity

Inactivity was the most commonly reported concern regarding the respondent's physical health. Some participants recalled being more active in the past.

> *"I haven't played sport since I finished college two years ago.* | **N14 (F, 24)**

Others reported that although they were physically active, it was their sedentary behaviour that was concerning them.

> *"I need to be more active. I do Zumba three times per week, but for the rest of the week I'm doing nothing except housework."* | **N07 (F, 45)**

Another participant expressed concern about not doing enough physical activity or exercise.

> *"My biggest concern is that I'm not going to the gym regularly enough. It's difficult after a long day at work to not get into a slump"* | **N12 (F22)**

iii. Pain

Pain was also a frequently reported health concern. Common causes of pain reported by participants included weight gain following diagnosis;

> “I am concerned about the weight that I’ve gained as it’s affecting me. I now have pain in my shoulders, hips, back and neck from the weight gain.” | **N04 (F, 24)**

A deleterious consequence of prolonged sedentary behaviour;

> *“I need to be more active. I’m studying for exams at the moment and just sitting at a desk all day is causing me shoulder and back pain.”* | **N11 (M, 22)**

Or longstanding musculoskeletal issues;

> "I have bulging discs in my spine, I have constant pain in my right hip." | **N06 (F, 42)**

Theme 5: Awareness of Abilities

Decline of Physical Performance

Several participants reported a decline in physical functioning since receiving their diagnosis. For some participants, the extent of this decline was identified following the completion of the test battery.

> *“I was surprised by the tests today, years ago I would have found them fine, but today they were very difficult. It felt like my body wasn’t strong enough.”* | **N18 (M, 25)**

For other participants, they could make direct comparisons between certain outcome measures and previous physical performance.

> *“I was disappointed to see how much my fitness has decreased, I used to be able to do 100 push ups per day, now I can barely do 10.”* | **N20 (M, 20)**

One participant reported that completion of the test battery made her aware of how quickly her physical performance declined.

> *"Eye-opening to say the least. .. It made me aware of how far you can regress in a short amount of time. 2 years ago I was going to the gym 4 days a week, I was 4 stone lighter than I am now."*| **N4 (F, 24)**

Difficulty of Tests

Several participants, irrespective of age or gender, reported considerable difficulty with the test battery.

> *"I am concerned about my fitness after today, I didn't think I would be panting that hard."* | **N15 (M, 20)**

Another participant expressed how exercising without distractions such as music made her aware of how her aerobic fitness had declined.

> *"I listen to music when I exercise and that would drown out the sounds of my heavy breathing, but today all I could focus on was that."* | **N07 (F, 45)**

One participant reported that completing the test battery actually encouraged them to improve their physical performance.

> *"These tests really showed me I need to focus on my fitness after my exams. Just because I haven't put on weight, doesn't mean that I am healthy. I am going to change"* | **N13 (F, 24)**

Theme 6: Role of Physiotherapy

Participants were asked for how they felt that physiotherapy could address the aforementioned concerns with their physical health. Responses included physiotherapist-designed exercise programmes, advice on how to reintroduce exercise, and providing external sources of motivation.

i. Advice on Reintroducing Exercise

Considerable difficulty was reported by participants when trying to reintroduce exercise following their diagnosis. This difficulty may be caused by a lack of education regarding exercise;

> *"I have no experience with exercise, I wouldn't know what to do. I think it would be great to improve my awareness and knowledge with exercise and show me how to ease into exercising." |* **N09 (M, 59)**

Another participant suggested that the content of the advice should focus on how to reincorporate exercise into their daily life.

> *"Advice on how to get back to exercising, how to fit it into your schedule, activities to do at home or around my community."* | **N14 (M, 43)**

ii. Physiotherapist Prescribed Exercise Programmes

Participants who were familiar with exercising expressed that they would like exercise programmes prescribed by a physiotherapist to complete independently.

> *"I'm fed up with doing the same exercises all the time. My knowledge regarding exercise is quite limited."* | **N16 (F, 63)**

Participants expressed that programmes should be designed to require little equipment to help overcome the financial barrier associated with gyms.

> *"I'd love physiotherapist-recommended exercises, something I can do at home to improve my fitness that doesn't require much equipment."* | **N02 (F, 36)**

Another participant suggested the provision of exercise programmes that varied in intensity to accommodate the fluctuating nature of fatigue in people with narcolepsy.

> *"Provision of "lighter" exercises would be useful. I feel it would help motivate you to do something if you're unable to complete an entire workout, that less is better than none."* | **N01 (F, 25)**

iii. External Source of Motivation to Promote Adherence

Difficulties with escaping the vicious cycle of sedentary behaviour was frequently reported by participants. This issue seemed to stem from a lack of motivation and challenges with making oneself accountable for engaging in regular exercise.

> *"It's easier to come up with an excuse than it is to exercise. If I need to be at a meeting, I physically need to be there. But with exercise it's self-directed, and I find myself taking the easy way out."* | **N21 (F, 44)**

With a lack of self-confidence being a major psychological barrier towards exercising as reported by participants, a common suggestion by participants to encourage exercise and promote adherence was one-to-one physiotherapy sessions.

> *"I would greatly appreciate one-to-one sessions to help gain confidence with exercising."* **| N08 (F, 26)**

One participant expressed how this external source of motivation would assist her in returning to exercise.

"I feel it would greatly improve my motivation to get back exercise, even just having someone check in would boost my commitment." | **N23 (F, 20)**

Chapter 5:
Discussion

This thesis explored physical performance in an outpatient population with narcolepsy. Additionally, it examined the relationship between physical performance variables, quality of life and symptom severity within this population and the perception of unmet physical needs, exercise habits and preferences.

5.1 Participant Recruitment and Characteristics

Just over half of participants were female (n=13, 56.5%), and the mean age of participants was 31.5 (± 13.2) years. These results are similar to those of the systematic review and meta-analysis presented in Chapter 2, which identified that 54.31% of participants were female, and the mean age was 40.8 years. The majority of participants in this study were aged 20-29 years. Nearly all of the recruited participants (n=22, 95.7%) were diagnosed with type 1 narcolepsy. The proportion of type 1 to type 2 Narcolepsy (95.7%: 4.3%), is considerably higher than that observed in the study by Matoulek et al. (2017) which observed a ratio of 76.2%: 23.8%, respectively. The lower proportion of type 2 narcolepsy may be attributable to the small sample size observed in this study.

Approximately two-thirds of participants were deemed overweight or obese (n=15, 65.22%) according to their BMI classification. This is similar to the general Irish population, of which 60% were overweight or obese (Healthy Ireland, 2019). The mean BMI of all recruited participants was 28.47 (± 6.82) Kg/m^2. This finding is similar to that observed the study by Matoulek et al. (2017), in which the mean BMI was 29.9 (± 5.7) Kg/m^2. Obesity has been shown to correlate with deleterious outcomes in people with narcolepsy. A study by Inocente et al. (2013) identified an earlier onset of sleepiness and cataplexy in obese children with narcolepsy, and lower sleep efficiency, a higher apnoea hypopnea index and respiratory arousals than nonobese children with narcolepsy. Furthermore, obesity was linked with feeling more tired and activity limitations manifesting as absences from school (Inocente et al., 2013).

For nearly half of the participants, the Leaving Certificate (n=11, 47.83%) was their highest educational achievement. This can be attributed to the young age of participants, as the majority (n=14, 60.87%) of participants were aged between 20-29 years. Furthermore, 47.83% (n=11) were currently enrolled in Third Level education. Of the recruited participants, only 39.13% (n=9) were in employment. In a study by Dodel et al. (2004) 59% of participants (n = 44) reported that they were unemployed, of which 43% (n = 32) named narcolepsy as the reason for being unemployed. The rate of unemployment was considerably lower in this sample (n=3, 13.04%), but this may be attributed to a high proportion of participants being in full-time education (n=14, 60.87%) due to the young age of the sample.

The majority of participants reported living with their family (n=19, 82.60%), whilst only two participants lived alone (8.70%) or with their partner (8.70%), respectively. The small number of participants that live alone could reflect the young age of the majority of participants or the independence of people with narcolepsy possibly being reduced or limited. It has been reported that the profound sedative effect of medications such as Sodium Oxybate may require people with narcolepsy to change living arrangements, particularly if they live alone (Thorpy and Dauvilliers, 2015, Wozniak and Quinnell, 2015).

5.2 Cardiopulmonary Fitness

Cardiopulmonary fitness was assessed using the YMCA Submaximal Bike Test. Participants' predicted VO_2 max was generally deemed below-average/average when compared to age-and-gender matched normative values. Participants in this study had higher predicted VO_2 max (39.0 mL.kg.min-1 ± 34.3) than the cohort with narcolepsy assessed in the study by Matoulek et al. (2017) (30.1 mL.kg.min-1 ± 7.5). However, this comparison must be cautiously interpreted, as this study used the YMCA submaximal bike test whilst the study by Matoulek et al. (2017) utilised maximal Cardiopulmonary exercise testing. The YMCA bike test provides a predicted VO_2 max based on an individuals' submaximal performance. This prediction has been reported to only be effective in predicting energy expenditure at submaximal intensities and can overestimate predicted VO_2 max at maximal efforts (Garatachea et al., 2007).

A significant negative correlation was identified between participant BMI and predicted VO_2 max, with cardiopulmonary fitness decreasing as BMI increased (r = -0.632, p=0.01). Although not causative, this finding is important as a high prevalence of obesity can be observed in people with narcolepsy, with approximately 75 percent of children with narcolepsy onset before puberty being classified as obese (Challamel et al., 1994). Recruited participants in this study had a mean BMI of 28.47 (±6.82) Kg/m^2. In general populations, weak negative correlations were identified between BMI and VO_2 max (r= -0.3232, p=0.0171).

A study by Matoulek et al. (2017) identified that cardiopulmonary fitness was inversely correlated to sleepiness severity and the number of cataplexy episodes per month. However, this correlation was not identified between predicted VO_2 max, and the incidence of general cataplexy ($r_s(21) = -0.213$, p=318), or partial cataplexy ($r_s(21) = -0.173$, p=0.328) as measured by the NSS in the present study. Furthermore, no significant correlation was identified between predicted VO_2 max and sleepiness severity ($r_s(21) = -0.056$, p=0.798) as measured by the ESS. With research by Messina et al. (2016) showing that cardiovascular exercise can improve the levels of plasma orexin-A in humans (the loss of which causes narcolepsy with cataplexy (Zhang et al., 2007)), further research is warranted to explore the relationship between narcolepsy-related symptoms and cardiopulmonary fitness.

5.3 Physical Activity and Sedentary behaviour

Physical activity and sedentary behaviour were subjectively assessed through the Physical Activity Vital Sign and the Sedentary Behaviour Questionnaire, and objectively through Actigraphy.

Considerable levels of agreement were identified between subjectively reported levels of exercise (40.00 ± 27.14 minutes) and objectively measured moderate-vigorous physical activity (42.20 ± 21.41 minutes). Similar levels of physical activity were observed in this sample (42.20 ± 21.41 minutes daily) than the unmedicated narcolepsy group (42.51 ± 10.33 minutes) and medicated narcolepsy group (49.44 ± 13.57 minutes) in a study by Bruck et al. (2005). This duration of physical is above the recommended threshold of 30 minutes of moderate-vigorous physical activity per day, as recommended by the World Health Organization (2010). However, considerably fewer steps were observed in this sample (3949.84 ± 2133.75 steps) than those obtained by adolescents with narcolepsy (7808.7 ± 3089.5) in the study by Parmar et al. (2019). The steps observed in this population are less than half of the recommended daily step count of 10,000 steps (Tudor-Locke et al., 2011). Unlike physical activity, a considerable mismatch was observed between subjectively reported and objectively measured sedentary behaviour. Participants reported twice as much subjective sedentary behaviour (20.42 hours) than objectively measured sedentary behaviour (10.21 hours). This mismatch can possibly be explained by overlapping sedentary activities being counted individually by the Sedentary Behaviour Questionnaire (e.g. listening to music or talking on the phone whilst working).

This reduced physical activity and high levels of sedentary behaviour can have deleterious impacts in people with narcolepsy and have been linked with higher BMI, poorer sleep quality, reduced night-sleep quality and duration, and increased frequency of napping (Filardi et al., 2018). Furthermore, prolonged sedentary behaviour has been shown to correlate with depression in people with narcolepsy (Parmar et al., 2019), and metabolic syndrome (Edwardson et al., 2012) and cardiovascular disease (Ford and Caspersen, 2012) in the general population. The reduced physical activity and step count observed in this population can possibly be explained due to sleep-related time constraints and social isolation, both of which are prevalent in people with narcolepsy (Kapella et al., 2015). These barriers were reflected in the open-ended responses obtained from participants, in which psychological barriers, fatigue and sleepiness were the most commonly cited barriers towards physical activity. Additionally, participants reported that although they were frequently engaging in exercise, they were considerably sedentary for the remainder of the day/week. Addressing these barriers and improving physical activity in this population should be prioritised, as reducing sedentary activity could potentially combat sleepiness in people with narcolepsy (Golden and Lipford, 2018).

5.4 Upper Limb

Muscle strength and endurance of the upper was assessed using dynamometry and the ACSM press up test, respectively.

Evident from the results, participants upper strength was lower than their age-and-gender-matched norms, with significant differences being observed between male participants and their matched comparators (p=0.05). The reduced grip strength observed in this population sample is concerning, as grip strength has been shown to correlate to several adverse outcomes. In men, lower grip strength has been associated with all-cause mortality, and cause-specific mortality from cardiovascular disease, all respiratory disease, chronic obstructive pulmonary disease, colorectal cancer, lung cancer and breast cancer (Celis-Morales et al., 2018). The differences between female participants and their age-and-gender-matched normative values were not statistically significant (p=0.12). From the qualitative interviews, participants reported an awareness of their reduced muscle strength. One participant expressed that they had “no strength in their arms” and felt that their grip strength was poor, whilst another described how their strength declined following their diagnosis of narcolepsy “*years ago I would have found them(the tests) fine, but today they were very difficult. It felt like my body wasn’t strong enough.”.* Interventions targeting improving the strength of this population should be incorporated, as grip strength is indicative of overall muscular strength and may protect from disability in older age as it can provide a safety margin above the threshold for disability (Rantanen et al., 1999).

Participants push up capacity was markedly reduced when compared to age-and-gender matched norms, with participants generally scoring the fair-needs improvement category. Longitudinal studies suggest that push up capacity is inversely related to the risk of cardiovascular disease, with individuals able to perform 11 or more push-ups having a significantly lower risk of future cardiovascular events (Yang et al., 2019). However, approximately two-thirds of participants (65.2%, n=15) failed to meet this threshold. Furthermore, a significant negative correlation was identified between participant age and push up performance (r = -0.458, p=0.05), with performance decreasing with age. For some participants, the Push Up test made them aware of how their physical functioning had declined since receiving their diagnosis: *“it was disappointing to see how my physical health has regressed, I used to be able to do 100 per day, now I could barely do 10”.* Improving muscle strength and endurance should be prioritised in people with narcolepsy, as both have been shown to provide independent protective against all-cause mortality and hypertension in healthy males and is inversely associated with metabolic syndrome incidence and prevalence (Artero et al., 2011). Improving muscular endurance should be prioritised in people with narcolepsy in an attempt to discourage the development of adverse chronic conditions in later life.

5.5 Lower Limb

Muscle strength and endurance of the upper was assessed using the Countermovement Jump Test and the Wall Squat Test, respectively.

The Countermovement Jump Test is used to evaluate lower limb strength (Liebermann and Katz, 2003) and the resultant jump height has been shown to correlate with maximal strength, and explosive strength (Nuzzo et al., 2008), speed (Wisloff et al., 2004), agility (Barnes et al., 2007) and power (Tricoli et al., 2005). The Countermovement Jump Test was the only physical outcome measure where performance varied considerably between age groups and genders. When compared to age-and-gender matched norms, participants in the 20-29 age group, regardless of gender, performed considerably lower than their matched normative values. Conversely, males aged 40-49, and 50-59, and females aged 40-49 scored higher than their matched normative values. However, there were very few participants in the males aged 40-49 and 50-59 age groups, and as such, these results must be cautiously interpreted. Given the small sample size of this study, further research is warranted to explore the lower limb strength of people with narcolepsy.

From the open-ended responses, participants frequently reported the wall squat as being the most challenging outcome measure, regardless of age. However, the reported difficulty associated with the wall squat test may be attributable to the order of the test battery, as the wall squat test was the final measure completed. Overall, participants had considerably less lower limb endurance than age-and-gender matched norms as measured by the Wall Squat test. Participants generally scored in the 25th-50th percentile for their age and gender. However, specific age groups performance was below the 25th percentile for their gender, in particular the 40-49 male and female groups, and the 30-39 female group. Additionally, this outcome measure provides an indication of the stability of the lower limb (Chimera et al., 2017). Furthermore, with wall squat performance being linked to heart rate and blood pressure (Goldring et al., 2014), lower limb endurance as measured by wall squat performance may provide an indication of cardiovascular health.

There was great difficulty in designing a test battery for a population in which these parameters have not been previously investigated. Although participants in this sample were generally young adults, the Narcolepsy Clinic in St. James's Hospital caters to adults with narcolepsy throughout all age groups. As such, selected outcome measures had to have normative data available for all age groups, whilst avoiding ceiling effects with more clinically orientated outcome measures. In selecting these outcome measures, the physical performance of this sample was able to be measured, however, the implications of these findings outside of comparing to population norms were limited.

5.6 Quality of Life

Summary

Participants reported considerably low HRQoL as measured by the SF36 and FOSQ. In particular, the Mental Component Summary scores (42.98) were lower than the Physical Component Summary scores (45.91). This finding suggests that narcolepsy has a greater impact on mental wellbeing than physical wellbeing in people with narcolepsy. However, the most affected HRQoL were primarily physical such as the Physical Role Limitations (45.99) domain of the SF36, and the Activity Levels (2.27) domain of the FOSQ. Participants also scored poorly in the Vitality (42.01) domain of the SF36. These results highlight that impairment with daily activities, fatigue and reduced energy levels is central to the lived experience associated with narcolepsy.

Comparison

Participants reported similar HRQoL to the pooled mean SF36 scores reported earlier in the meta-analysis in Chapter Two (Table 2). The aforementioned pooled mean scores represent a sample of 4600 people with narcolepsy. Participants scored higher than the normative narcolepsy group in the following SF36 domains: Physical Functioning, Bodily Pain, General Health, Social Functioning and Mental Health. Similarly, participants reported lower scores in the Physical Role Limitations, Emotional Role Limitations, Vitality, and the Physical and Mental Component Summary domains of the SF36. When compared to the general population, participants reported poorer quality of life than population norms of the US, UK, France and Norway (Figure 29).

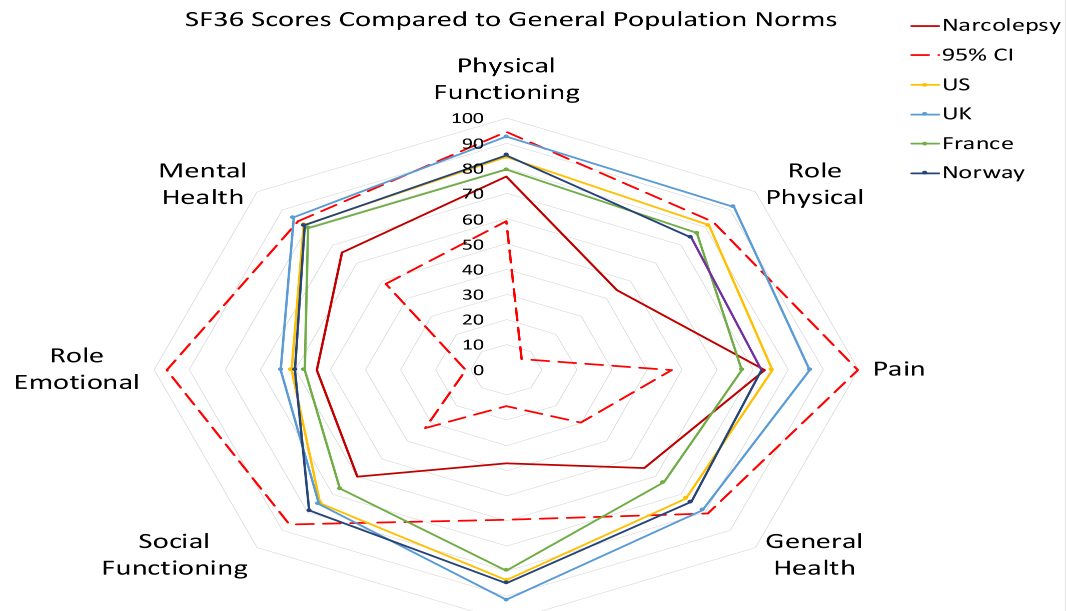


Figure 29: SF36 Scores Compared to General Population Norms

Similarly, the reported HRQoL of participants was compared to the HRQoL of normative values obtained from people with epilepsy, diabetes, multiple sclerosis and hypertension (Figure 30). Participants experienced consistently lower levels of Vitality, Mental Health, Emotional Role Limitations, and Social Functioning when compared to the aforementioned chronic health conditions. Vitality and Emotional Role Limitations observed the most significant difference between participant scores and scores obtained from the chronic health conditions.

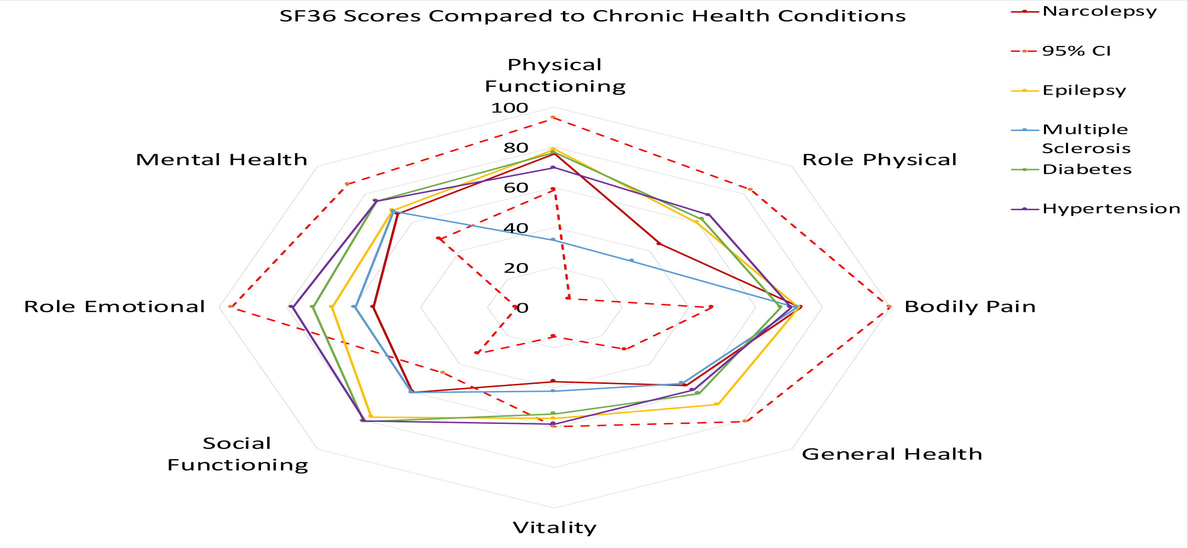


Figure 30: SF36 Scores Compared Chronic Health Conditions

Regarding the FOSQ, participants reported lower quality of life than older adults aged over 65 obtained from a study by Gooneratne et al. (2003). Given the relatively young age of the participants enrolled in this study (31.52 years ±13.17), this finding is important and highlights the deleterious impact that narcolepsy has on HRQoL (Figure 31).

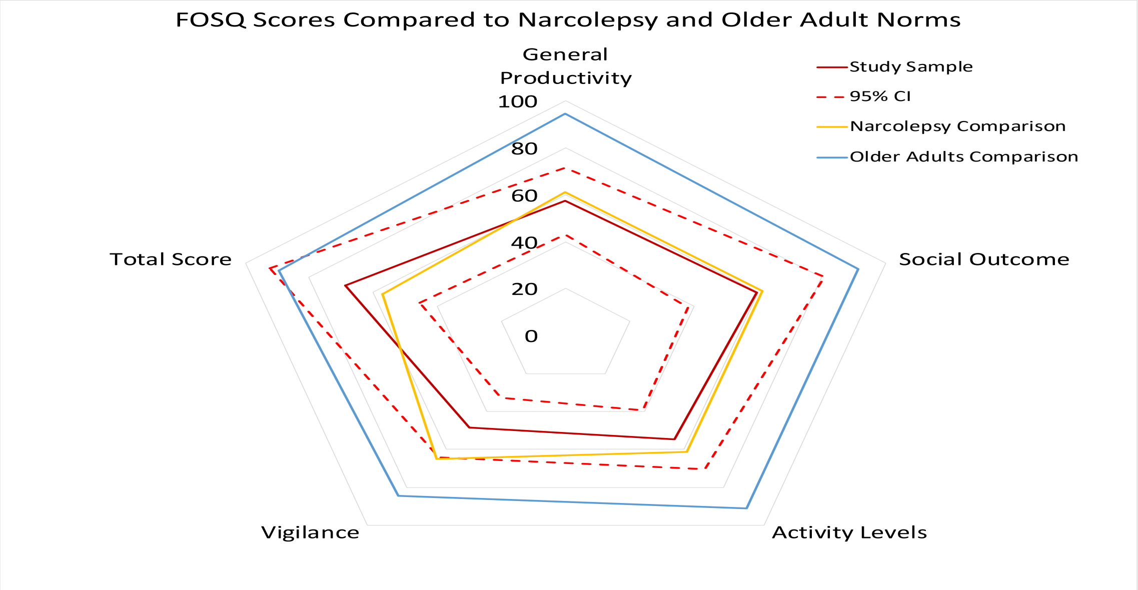


Figure 31: FOSQ Results Compared to Narcolepsy and Older Adult Normative Values

Discrepancy Between Physical Functioning and Physical Role Limitations

There was a considerable mismatch between the reported physical wellbeing and the impairments that arise due to physical wellbeing. Physical Functioning was the second least affected domain of the SF36 (76.74). However, considerable Physical Role Limitations were reported (55.30). This finding was consistent with the pooled mean results of the meta-analysis reported in Chapter 2, with less impairment reported in Physical Functioning (67.84) than with Physical Role Limitations (45.99). These findings suggest that although participants may perceive their overall physical wellbeing to be acceptable, they are cognizant of how it impacts their abilities to perform daily tasks such as dressing, walking, and climbing stairs.

Implications

The interrelationship between physical functioning and psychiatric wellbeing in people with narcolepsy suggested by Morse and Sanjeev (2018) could potentially explain the reduced mental and physical wellbeing observed in this sample and in people with narcolepsy. Less physical activity in people with narcolepsy has been linked to lower mood (Bruck et al., 2005), and considerable levels of sedentary behaviour were observed in this sample. This reduced physical activity can contribute to the development of a vicious cycle where inactivity contributes to increased sleepiness (Golden and Lipford, 2018). Consequently, this worsening of symptoms can contribute to the reduction of habitual physical activity and quality of life (Matoulek et al., 2017). Given the multimodal impact of narcolepsy on overall wellbeing, improving HRQoL should be prioritised, particularly as maintaining a healthy balance in life was the most frequently reported priority by participants.

5.7 Symptom Severity

Participants expressed a significant symptom burden as measured by the Narcolepsy Severity Scale and the Epworth Sleepiness Scale.

Excessive Daytime Sleepiness

Sleep attacks were the most frequently experienced symptom, occurring daily for 56.5% of respondents (n=13). The mean ESS score was 15.57 (± 4.58), which indicates moderate sleepiness severity. Furthermore, sleep attacks were identified as the most severe symptom of narcolepsy (60.52 ± 22.41) and over half of the respondents (56.5%) were concerned about suddenly falling asleep throughout the day without noticing. In a study by Teixeira et al. (2004), 67% of respondents reported falling asleep in a workplace setting. Furthermore, 52% of participants reported that they had left a job because of narcolepsy (Teixeira et al., 2004). Similar accounts were observed in the open-ended responses, where two participants reported that they had changed careers to occupations that were more manageable with their condition. In a study by Dodel et al. (2004) 59% of participants (n = 44) reported that they were unemployed, of which 43% (n = 32) named narcolepsy as the reason for being unemployed. Of those assessed in this study, only nine participants (39.13%) reported being employed, and 11 were currently enrolled as students (n=11, 47.83%). Even with those who are employed, work-related productivity is also affected in people with narcolepsy and higher costs relating to absenteeism ($7631 vs $12,839, P<0.001) and presenteeism ($4987 vs $7013; P <.001) have been observed when compared to matched controls (Flores et al., 2016).

Cataplexy

Nearly all of the recruited participants (n=22, 95.65%) were diagnosed with Type 1 Narcolepsy. The proportion of Type 1 to Type 2 Narcolepsy (95.65%: 4.35%), is considerably higher than that observed by the study by Matoulek et al. (2017) which observed a ratio of 76.20%: 23.80%, respectively. Cataplexy was reported as the second most severe symptom, with over half of participants (57.89%) reported that cataplexy affected their work, social or family life. This is an important observation, as a study by Thorpy et al. (2019) found that only 12.5% of people with narcolepsy, compared to 70.5% of physicians, reported cataplexy as being a disruptive symptom. General and Partial Cataplexy were both experienced at least monthly in 56.4% of respondents (n=13), which is lower than the 67% observed in the study conducted by Ingravallo et al. (2012). Cataplexy can cause significant disruption to a person’s life, with 93.6% of physicians reporting that people with narcolepsy alter their lives, oftentimes unknowingly, to accommodate their symptoms (Thorpy et al., 2019). The social wellbeing of people with narcolepsy can be considerably affected in people with narcolepsy, with significantly more feelings of social rejection, financial insecurity, internalised shame and social isolation being reported than in people without narcolepsy (Kapella et al., 2015). Furthermore, 40% of people with narcolepsy in a previous study reported avoiding social situations, and 20.0% reported avoiding strong emotions (Thorpy et al., 2019). Several participants reported reducing their engagement in exercise due to concerns over cataplexy. This social withdrawal can predispose to the development of psychiatric disorders such as depression, and Morse and Sanjeev (2018) propose the concept that narcolepsy shares similar pathophysiology with psychiatric conditions such as depression and anxiety. This significant symptom burden needs to be addressed to improve the physical, mental and social wellbeing of people with narcolepsy.

Implications

Narcolepsy is a condition that can significantly affect an individual's overall functioning by imparting a deleterious effect on their social wellbeing and physical wellbeing (Schiappa et al., 2018). Furthermore, the significant stigma associated with narcolepsy in young adults can contribute to the depression, academic and employment difficulties, and personal and social issues reported by this population (Kapella et al., 2015). Additionally, time constraints relating to narcolepsy-related symptoms can considerably limit the opportunities to engage in social interactions (Kapella et al., 2015). One participant described this difficulty as "You only have a limited amount of energy, so oftentimes I have to choose between socialising or studying." Several participants reported experiencing a significant decline in their physical, mental and social wellbeing shortly following the onset of narcolepsy-related symptoms. A study by Dauvilliers et al. (2001) identified the age of onset of narcolepsy symptoms in two large patient populations to peak at 14.7 years, and later in life at 35 years. This early symptom onset during the initial peak can be problematic, as paediatric narcolepsy is associated with comorbidities such as rapid weight gain, precocious puberty, and adversely affected social functioning, depression and anxiety (Plazzi et al., 2018).

A possible explanation for this decline in wellbeing could be the prolonged diagnostic delay observed in people with narcolepsy, which in turn delays treatment to manage the condition and can affect the burden of disease (Thorpy and Krieger, 2014). This diagnostic delay varies according to gender, with 85% of men likely to receive a diagnosis within 16 years after symptom onset, compared to 28 years in women, despite similar symptom presentation (Won et al., 2014). Few longitudinal studies have explored the wellbeing of people with narcolepsy over time. However, the findings from studies by Vignatelli et al. (2004) and Vignatelli et al. (2011) identified that there was no significant difference in HRQoL as measured by the SF36 domain scores and only slight declines in the component summaries. Further research is warranted to explore the effects of ageing on symptom severity and quality of life in people with narcolepsy.

5.8 Exploratory Outcomes

The age, gender and BMI of this sample were explored to identify how these factors correlated with physical performance, symptom severity, and quality of life in people with narcolepsy. Correlations relating to BMI and age were conducted using Spearman's correlation, whilst between-group differences to identify the influence of gender were accomplished using the Mann Whitney U test.

Age

Age was found to negatively correlate with Total FOSQ scores, with HRQoL decreasing with advancing age (rs(21) = -0.465, p=0.05). This contrasted with the findings of the meta-analysis previously reported, where increasing age was found to positively associate with the physical functioning, physical role limitations, bodily pain, emotional role limitations (p=0.05), and social functioning (p=0.01) domains of the SF36. This furthers the aforementioned ambiguity surrounding the influence of ageing on HRQoL, particularly as there have been few longitudinal studies have explored the wellbeing of people with narcolepsy over time. The findings from studies by Vignatelli et al. (2004) and Vignatelli et al. (2011) identified that there was no significant difference in HRQoL as measured by the SF36 domain scores and only slight declines in the component summaries. This decline in HRQoL with ageing coincides with an observed decline in physical functioning, with significant negative correlations identified between age and push up performance (rs(21) = -0.0458, p=0.05), with performance decreasing with age. In a study by Matoulek et al. (2017) that explored cardiopulmonary fitness in people with narcolepsy, significant correlations were identified between participant age and VO2peak% (p=0.039), and VO2peakSD (p=0.030). In line with the recommendations of the systematic review and meta-analysis, further research is necessary to explore the influence of ageing on HRQoL in people with narcolepsy.

BMI

Diagnosis is often accompanied by rapid weight gain, and high incidences of obesity have been reported in people with narcolepsy compared to the general population (Dahmen et al., 2001). Several participants reported gaining considerable amounts of weight following their diagnosis, ranging from 12.7 Kg to 63.5 Kg. This increased weight associated with narcolepsy can result in negative body image issues for people with narcolepsy "I don't like the way I look; I am self-conscious about my weight". BMI appears to have insignificant effects on symptom severity, as measured by the NSS (r = 0.119, p=0.588) and the ESS (r = -0.148, p=0.499). This finding supports that of a study by Dahmen et al. (2001), in which BMI in people with narcolepsy was not affected by EDS severity, cataplexy frequency, hallucinations, sleep paralysis or automatic behaviours. This finding also supports the theory that excessive daytime sleepiness does not appear to account for the increased BMI and excess body fat observed in people with narcolepsy, as despite overlapping symptom presentation, people with idiopathic hypersomnia typically have lower BMIs (Kok et al., 2003). The effect of BMI on physical performance appears to be deleterious, and significant negative correlations identified were between BMI, and predicted VO2 max (r = -0.632, p=0.01), and wall squat performance (r = -0.632, p=0.01). Future research is warranted to explore how BMI influences physical performance and symptom severity in people with narcolepsy, particularly between type 1 and type 2 narcolepsy.

Gender

Symptom severity in this sample appeared not to be significantly affected by gender in this sample. No significant between-group differences were identified between males and females for both total Narcolepsy Severity Scale scores or Epworth Sleepiness Scale Scores. This finding is consistent with the study conducted by Won et al. (2014), where men and women were found to report similar levels of subjective sleepiness as measured by the Epworth Sleepiness Scale (mean 16.2 ± 4.5; p = 0.18). Regarding health-related quality of life, no significant correlations or between-group differences were identified between males and females. From the systematic review and meta-analysis presented in Chapter 2 (Table 1), few studies explored the influence of gender on HRQoL in people with narcolepsy. Further research is warranted to explore this concept, as gender has been shown to affect important features in narcolepsy such as diagnostic delays and symptom severity (Won et al., 2014).

5.9 Main Findings

Considerably poor physical performance, quality of life and symptom severity were observed in this population, irrespective of age, gender and BMI. Physical performance, which consisted of an assessment of the following domains; cardiopulmonary fitness, physical activity, muscle strength and muscle endurance, was markedly reduced throughout and considerably lower than population norms. Similarly, HRQoL was markedly reduced when compared to general population norms and other chronic conditions such as epilepsy and hypertension, highlighting the burden of narcolepsy. Although we could not establish causation, strong correlations were identified between physical performance and quality of life, and symptom severity and quality of life. An illustration that represents the interrelationship identified between the aforementioned endpoints can be found below (Figure 32). Furthermore, considerably high levels of sedentary behaviour and a low step count was observed in this sample. As this was the first study to comprehensively investigate physical performance in this population, it was challenging to develop a test battery. There was little surrounding literature to aid with selecting outcome measures for this cohort. Given the broad age range of those attending the narcolepsy clinic, selected measures required normative data for both males and females throughout all age groups to enable comparison with population norms.

An experimental battery of subjective and objective outcome measures was trialled during this study. There was the preconception that this population would be challenging to work with, primarily fuelled by the media's portrayal of people with narcolepsy as being lazy or unmotivated or humorously falling asleep (Flygare and Parthasarathy, 2015). In reality, participants were eager and enthusiastic to participate in this study, and from the open-ended responses, participants were aware of their physical health needs. The attitudes towards participation and physical activity observed by participants suggest that future research within this population would be feasible.

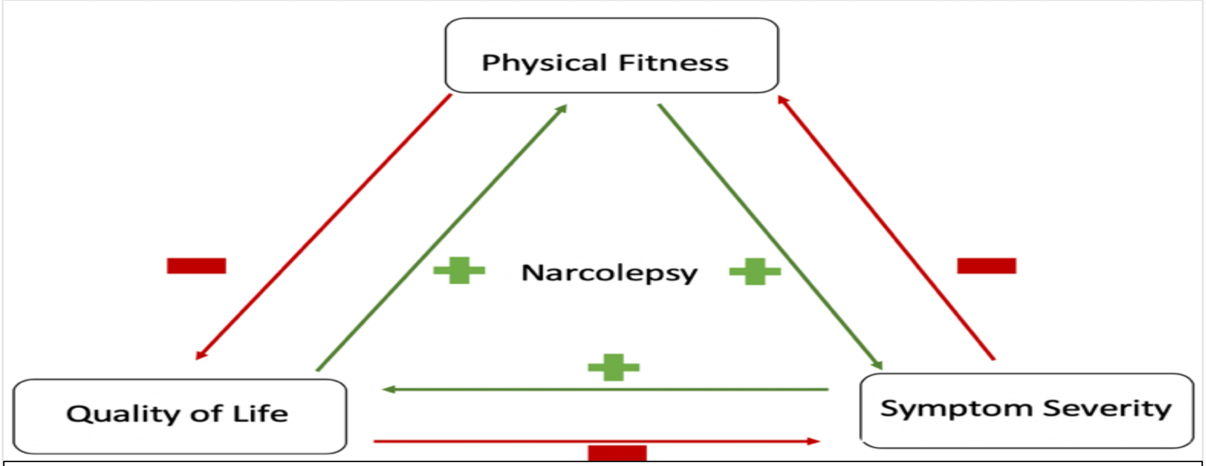


Figure 31: Relationship Between Physical Performance, Symptom Severity and Quality of Life in Narcolepsy

5.10 Clinical Recommendations

Clinicians interacting with people with narcolepsy should upskill their abilities in providing advice to their patients on the introduction of exercise and physical activity into their daily lives. People with narcolepsy should be advised to gradually improve their exercise duration to meet the World Health Organization (2010) recommendation of performing 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity. Muscle-strengthening activities should be done involving major muscle groups on two or more days a week (World Health Organization, 2010). Strategies to reduce sedentary behaviour to discourage excessive daytime sleepiness in this population should be incorporated. In a study conducted by Krahn and Rogers (2015), physical exertion in the form of walking around was reported to be the most effective manner of reducing excessive daytime sleepiness and was endorsed by 73% of those surveyed. Reducing sedentary behaviour in an attempt to improve physical activity levels in narcolepsy could help preserve physical functioning, thus discouraging the development of psychiatric symptoms and further deterioration of function and quality of life (Morse and Sanjeev, 2018). The promotion of physical activity and the reduction of sedentary behaviour should be encouraged by all clinicians involved in the care of people with narcolepsy. As low step counts noted in this sample, pedometers could potentially be used to promote physical activity within this population.

5.11 Future Directions: Developing the Role of Physiotherapy

Exercise has the potential to be a powerful non-pharmacological management strategy for people with narcolepsy. A bidirectional relationship between physical activity and sleep has been identified, with physical activity demonstrating the ability to improve sleeping and promote wakefulness, and poor sleep resulting in reduced physical activity (Kline, 2014). Additionally, physical activity is associated with longer sleep duration, higher sleep quality, reduced BMI and nap frequencies in people with narcolepsy (Filardi et al., 2018). People with narcolepsy are generally not referred to physiotherapists for specialised exercise recommendations. Given their expertise in exercise prescription, the potential role of physiotherapists in the interdisciplinary management of narcolepsy is promising. However, a significant knowledge gap must first be overcome, as the awareness of physiotherapists regarding the management of sleep disorders is considerably limited. Potential strategies to overcome this knowledge gap in physiotherapists is to increase the education of sleep disorders at an undergraduate. From the open-ended responses, participants identified that issues that they perceived a physiotherapist could assist them with addressing, namely advice of exercise, physical activity and lifestyle behaviour change. Further research is warranted in this cohort to assist in justifying the role of physiotherapy in the management of narcolepsy. This additional research should focus on:

- Establishing the barriers and facilitators to exercise for people with narcolepsy,
- Establishing the optimal dosage and how best to deliver an exercise intervention to explore the modulating effects of exercise on narcolepsy-related symptoms in this cohort.

Future Directions: Recommend Outcome Measures

There was considerable difficulty with selecting the test battery for this population. Although participants were concentrated in the 20-30 age group, there was a wide age range observed in this population. Outcome measures were selected based on having normative values for all age groups to enable comparison with population norms. A number of outcome measures selected for this study were not appropriate. Certain outcome measures such as the Wall Squat test, the Countermovement Jump test and the ACSM Push Up test proved to be difficult for older participants, given the natural declines in physical performance associated with ageing (Milanovic et al., 2013). Repetition-maximum tests may be more appropriate for the assessment of the upper and lower limbs. Additionally, the decision to use the YMCA Submaximal Bike test both positively and negatively affected this study. The YMCA Submaximal Bike has been shown to overestimate predicted VO_2 values (Garatachea et al., 2007). However, the YMCA Submaximal Bike test is a relatively short cardiopulmonary fitness test, taking approximately 15 minutes to complete, which greatly alleviated timing-related concerns. This additional time was beneficial, given the overall length of the test battery. Table 15 outlines the recommended outcome measures for future studies in this population based on the findings of this present study.

Table 15: Recommended Outcome Measures for Future Studies

Subjective Outcome Measures	**Construct Measured**
Short Form 36	Generic HRQoL
Functional Outcomes of Sleep Questionnaire	Sleep Disorder HRQoL
Narcolepsy Severity Scale	Symptom Severity
Epworth Sleepiness Scale	Symptom Severity
International Physical Activity Questionnaire	Physical Activity
Objective Outcome Measures	
Cardiopulmonary Exercise Testing (Maximal)	Aerobic Fitness
Actigraphy	Physical Activity
Dynamometry	Grip Strength
Predicted-1RM (Upper limb)	Strength Upper limb
Predicted-1RM (Lower limb)	Strength Lower limb

Future Directions: Recommend Assessment Structure

Excluding Covid-19 restrictions, the largest barrier to recruitment was that the timing of the assessment was too late (n = 6). Given that this was an evening clinic, and study appointments were frequently after participants' clinical appointments, study appointments were often late into the evening. Additionally, due to waiting times and travel duration, participants were oftentimes considerably fatigued by the time of their study appointment. Based upon conducting this study, several strategies could be employed to overcome these barriers and increase participation with this population.

i. Accounting for the timing of the assessment is vital, as many attendants of the clinic were reliant on public transport. If participants are travelling long distances to attend their clinical appointment, ensure that they are aware of ongoing studies and provide them with the opportunity to be assessed on the same day. Researchers should be flexible when providing assessment times to participants and work around the participants' schedule. Furthermore, study appointment scheduled prior to their clinical appointment could potentially limit the impact of fatigue on participant performance.

ii. Reducing the work participants need to complete in one sitting can potentially decrease the impact of fatigue on performance. Although having previously confirmed their participation prior to their appointment, the fluctuating nature of sleepiness and fatigue in narcolepsy may prevent participation on the day of the assessment. Several participants reported difficulty completing the questionnaires at the end of the test battery, either due to sleepiness, fatigue or reduced concentration. Strategies to overcome this issue include providing questionnaires to participants in waiting areas prior to their appointment or giving participants the option to receive or return questionnaires by post.

5.12 Study Strengths

This study had several strengths. Firstly, this novel study was conducted in a relatively understudied population. This study provided an insight into the physical performance of this cohort and explored the correlation between physical performance, symptom severity and quality of life. Furthermore, this study utilised broad and inclusive outcome measures which ensured that comparisons could be made with population norms and other chronic conditions.

5.13 Limitations

A major limitation of this study was the small sample size recruited (n = 23). Data collection for this study ceased twelve weeks early due to Covid-19 restrictions. An additional 14 participants had consented but were unable to be assessed due to the aforementioned precautions. Furthermore, the ages of those recruited were unevenly distributed, with participants generally concentrated in the 20-30s age group (n = 14, 60.87%). However, the remaining age groups had much fewer participants, with the 50-59, and 60-69 age groups only having one participant each. As a result, the ability to derive conclusions was severely limited, and the results obtained from this must be considered cautiously, particularly in the older age groups.

As this was a cross-sectional study, participants were assessed at a single timepoint. All data was initially presented descriptively to provide an insight into the physical and mental wellbeing of participants. The analysis of collected data must be cautiously interpreted when attempting to derive causal relationships from the cross-sectional analysis. Furthermore, as participants were only assessed at a single timepoint, performance may not be wholly indicative of their overall physical performance and could be influenced by an exacerbation of symptoms such as excessive daytime sleepiness. Additionally, the primary researcher (RT) both recruited and assessed all participants, and the biases that arise consequently must be considered.

Another major limitation of this study was the low compliance with Actigraphy, as only 54.17% (n=13) of the sample completed this measure. Actigraphy was the only outcome measure not to have complete compliance. The combination of equipment shortages and Covid-19 precautions considerably reduced the opportunities to gather this actigraph data from participants. This low compliance could possibly be attributed to the requirement for participants to wear the actigraphs consistently for one week and could not be completed on the same day as the other outcome measures. Additionally, the short duration that participants were required to wear an actigraph may have resulted in an exaggerated measure of physical activity with participants consciously or subconsciously increasing their physical activity levels. Consequently, the analysis of objective physical activity and sedentary behaviour must be cautiously interpreted as it may not be fully representative of the sample.

Furthermore, participation bias must be considered, as individuals who agreed to participate may have been more actively pursuing strategies to optimise their physical wellbeing already. Consequently, the results obtained from this sample must be cautiously interpreted as they may not be wholly representative of the general population of people with narcolepsy.

5.14 Conclusion

In conclusion, this study profiled the physical performance of people with narcolepsy and explored the correlation between physical performance, quality of life and symptom severity. Additionally, this study trialled a physical test battery in a largely understudied population and provided recommendations for future research in this field.

More females than males participated in this study, and the mean age of participants was 31.52 years. Physical performance, which consisted of measurement of the following constructs; cardiopulmonary fitness, physical activity, muscle strength and muscle endurance, was markedly reduced in this sample when compared to population norms. Furthermore, HRQoL was also significantly lower than the general population and chronic conditions such as diabetes, hypertension, and epilepsy. The impaired physical and mental wellbeing observed in this sample was present irrespective of participant age and gender. An interrelationship was identified between physical performance, HRQoL and symptom severity. The selected outcome measures for this study were largely suitable. However, the Wall Squat Test and Countermovement Jump Test may not be the most accessible outcome measure for older participants, and comparisons were limited as a result. Repetition-maximum strength tests for the upper and lower limb may be more appropriate in future studies. All participants completed the subjective measures, which provided a valuable insight into the lived experience of narcolepsy and the barriers towards exercise in this population.

In summary, this sample of people with narcolepsy had considerably poor physical performance, quality of life and symptom severity. The interrelationship present between physical performance and important treatment endpoints such as HRQoL and symptom severity provides a potential avenue for the role of exercise and physiotherapy in the interdisciplinary management of this condition. Additionally, this population was both enthusiastic and receptive towards the study, proving that conducting physically orientated research within this population is feasible. Future research should explore the modulating effects of exercise in an attempt to address the poor physical performance, quality of life and symptom severity in people with narcolepsy.

Chapter 6:
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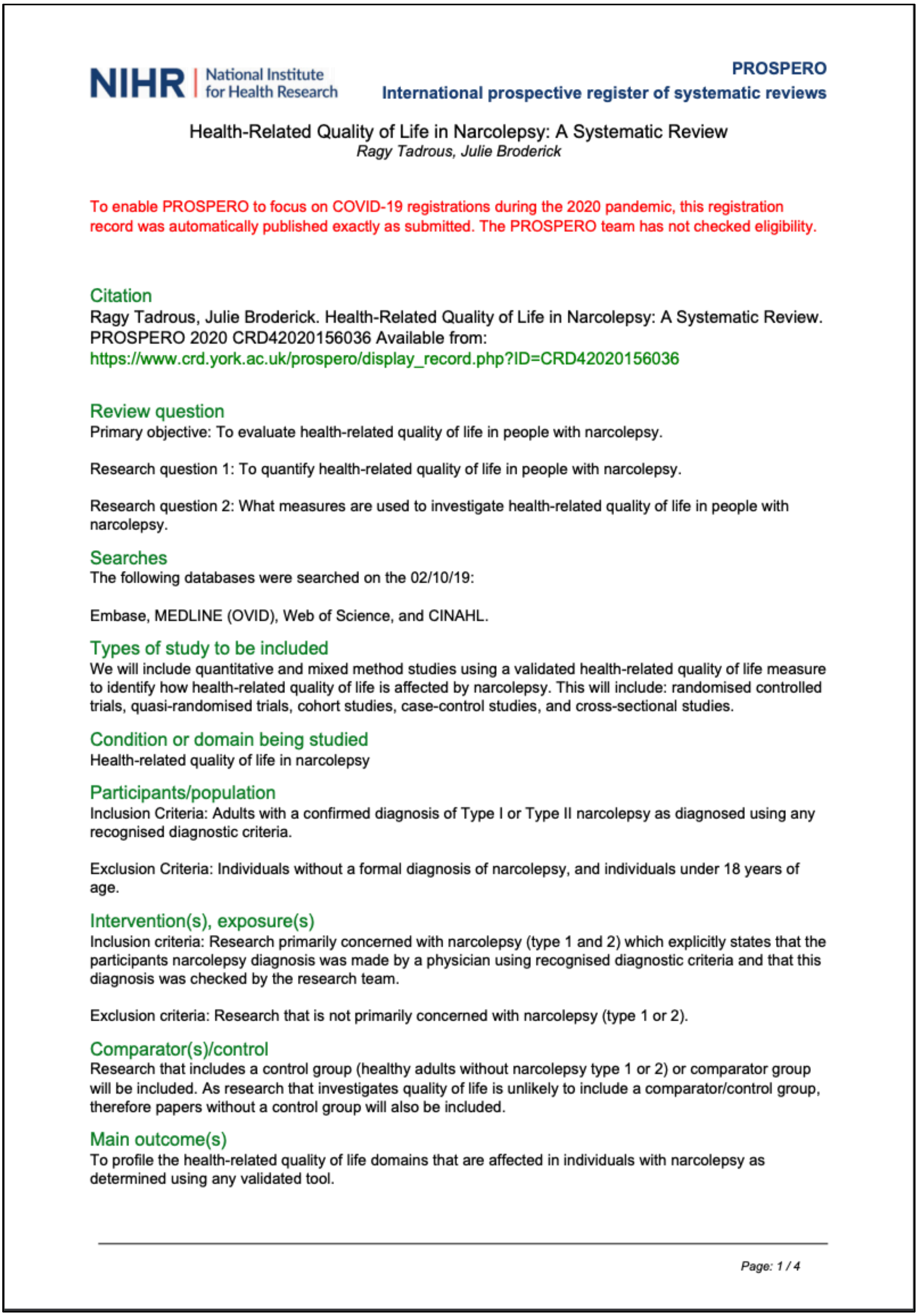
Chapter 8:
Appendices

Appendices

Appendix I: Systematic Review Registered with PROSPERO



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PROSPERO
International prospective register of systematic reviews

Health-Related Quality of Life in Narcolepsy: A Systematic Review
Ragy Tadrous, Julie Broderick

To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility.

Citation

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Review question

Primary objective: To evaluate health-related quality of life in people with narcolepsy.

Research question 1: To quantify health-related quality of life in people with narcolepsy.

Research question 2: What measures are used to investigate health-related quality of life in people with narcolepsy.

Searches

The following databases were searched on the 02/10/19:

Embase, MEDLINE (OVID), Web of Science, and CINAHL.

Types of study to be included

We will include quantitative and mixed method studies using a validated health-related quality of life measure to identify how health-related quality of life is affected by narcolepsy. This will include: randomised controlled trials, quasi-randomised trials, cohort studies, case-control studies, and cross-sectional studies.

Condition or domain being studied

Health-related quality of life in narcolepsy

Participants/population

Inclusion Criteria: Adults with a confirmed diagnosis of Type I or Type II narcolepsy as diagnosed using any recognised diagnostic criteria.

Exclusion Criteria: Individuals without a formal diagnosis of narcolepsy, and individuals under 18 years of age.

Intervention(s), exposure(s)

Inclusion criteria: Research primarily concerned with narcolepsy (type 1 and 2) which explicitly states that the participants narcolepsy diagnosis was made by a physician using recognised diagnostic criteria and that this diagnosis was checked by the research team.

Exclusion criteria: Research that is not primarily concerned with narcolepsy (type 1 or 2).

Comparator(s)/control

Research that includes a control group (healthy adults without narcolepsy type 1 or 2) or comparator group will be included. As research that investigates quality of life is unlikely to include a comparator/control group, therefore papers without a control group will also be included.

Main outcome(s)

To profile the health-related quality of life domains that are affected in individuals with narcolepsy as determined using any validated tool.

* Measures of effect

Outcomes taken at baseline or post intervention (if applicable) will be included.

Additional outcome(s)

To determine what measures are used to investigate health-related quality of life in people with narcolepsy.

* Measures of effect

Any validated health-related quality of life outcome measure will be included.

Data extraction (selection and coding)

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two authors to identify studies that potentially meet the inclusion and exclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers. Any disagreement between them over the eligibility of particular studies will be resolved through discussion between the two reviewers until an agreement has been reached.

Risk of bias (quality) assessment

Due to the varied quality and types of the articles retrieved in this review will be used. The quality of individual studies will be assessed through the use of the Quality Assessment Tool for Reviewing Studies with Diverse Design (QATSDD) (Sirriyeh et al. 2012). The QATSDD is a validated quality assessment tool that is applicable to research with heterogenous study designs including quantitative, qualitative and mixed method studies.

Strategy for data synthesis

Data obtained from the data extraction phase will be collated, and the study characteristics will be presented in table format. A narrative summary technique will be used to report the findings according to the domains of the health-related quality of life measures utilised.

Depending on the homogeneity of the included studies, the outcome measures utilised and the provision of sufficient quantitative data, a meta-analysis will be conducted. However, if there is significant heterogeneity present, a narrative synthesis will instead be performed. This narrative synthesis would focus on the study design, participant characteristics, the health-related outcome measure utilised and the quality of each study.

Analysis of subgroups or subsets

If the necessary data is available, subgroup analyses will be done for people with narcolepsy with cataplexy and narcolepsy without cataplexy separately, and individuals with vaccine-associated narcolepsy.

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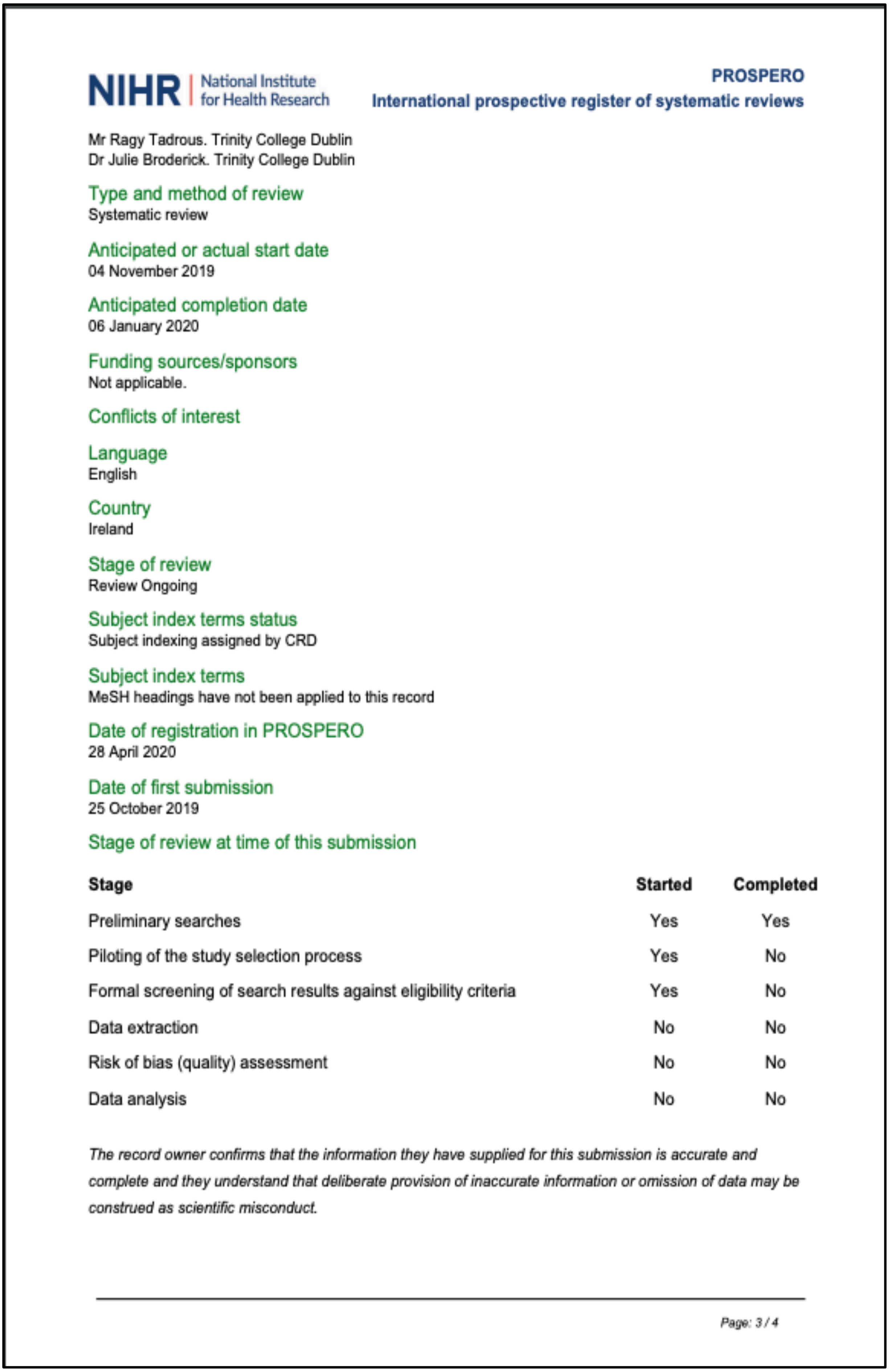
Review team members and their organisational affiliations



Mr Ragy Tadrous. Trinity College Dublin
Dr Julie Broderick. Trinity College Dublin

Type and method of review

Systematic review

Anticipated or actual start date

04 November 2019

Anticipated completion date

06 January 2020

Funding sources/sponsors

Not applicable.

Conflicts of interest

Language

English

Country

Ireland

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

28 April 2020

Date of first submission

25 October 2019

Stage of review at time of this submission

Stage	**Started**	**Completed**
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

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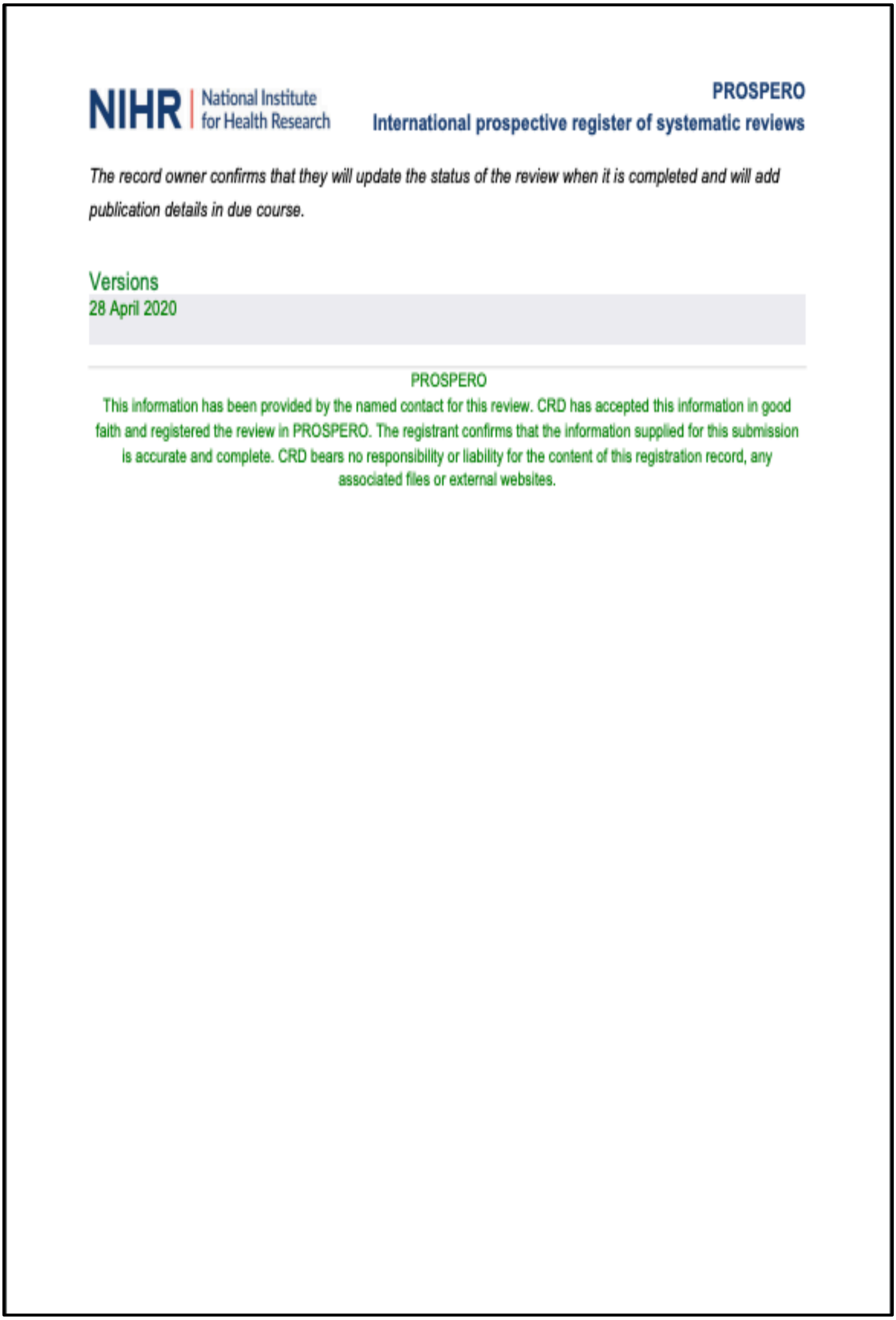

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Versions

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Appendix II: Health-related quality of life in narcolepsy: A systematic review and meta-analysis

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REVIEW ARTICLE

Health-related quality of life in narcolepsy: A systematic review and meta-analysis

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Summary

To date, there has been no systematic analysis of the literature regarding health-related quality of life in narcolepsy. This systematic review aimed to examine the impact of narcolepsy on health-related quality of life, measured through standardised health-related quality of life questionnaires such as the Short Form 36 and Functional Outcome of Sleep Questionnaire. The following databases: Medline, Embase, Cinahl, and Web of Science were searched for studies that investigated health-related quality of life in adults with narcolepsy. Studies were reviewed independently by two reviewers, and a random-effects meta-analysis was performed. A total of 30 studies were eligible for inclusion in the review. Additionally, meta-analyses were conducted for the Short Form 36 and the EQ5D. The Short Form 36 meta-analysis identified that the pooled mean scores for the Physical Component Summary (45.91) were less affected than the Mental Component Summary (42.98). People with narcolepsy experience substantially lower health-related quality of life when compared with the general population norms of the USA, UK, France and Norway, as well as compared with people with chronic diseases such as multiple sclerosis, diabetes, hypertension and epilepsy. Further research is warranted to identify the longitudinal effects of narcolepsy on health-related quality of life, and to develop a narcolepsy-specific health-related quality of life tool.

KEYWORDS
narcolepsy, quality of life, health-related quality of life

1 | INTRODUCTION

Narcolepsy is a rare, disabling chronic neurological disorder that is characterised by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations and sleep paralysis. Narcolepsy can be classified into two subtypes: type 1 narcolepsy (NT1) and type 2 narcolepsy (NT2), both of which have similar clinical presentations. However, NT1 can be distinguished by the presence of cataplexy, which is defined as an episodic loss of muscle tone in full consciousness that typically arises following intense emotions such as laughter or anger and decreased cerebrospinal fluid levels of hypocretin (Sateia, 2014). The incidence of narcolepsy is estimated to be 25–50 per 100,000 in Western populations (Overeem, Black, & Lammers, 2008). Symptom onset typically occurs in adolescence; however, approximately one-third of

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Prospero Registration URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=156036

people with narcolepsy experience initial symptoms in adulthood (Dauvilliers et al., 2001).

Health-related quality of life (HRQoL) can be described as a "multidimensional concept that includes subjective reports of symptoms, side effects, functioning in multiple life domains, and general perceptions of life satisfaction and quality" (Revicki, Kleinman, & Cella, 2014). Narcolepsy is a neurological condition that can predispose to the development of social and occupational dysfunction (Morse & Sanjeev, 2018). This condition has been associated with considerable detriment to daily life, including impaired quality of life, occupational and academic difficulties, and adversely affected social and personal relationships (Emsellem et al., 2020; Flores, Villa, Black, Chervin, & Witt, 2016; Kapella et al., 2015). With significant correlations identified between symptom severity and HRQoL (Dauvilliers et al., 2017), mitigating the deleterious effect of narcolepsy on HRQoL should be a critical therapeutic goal for people with narcolepsy.

Despite the frequent inclusion of HRQoL as an outcome measure in narcolepsy trials; to date, there has been no systematic review and meta-analysis to synthesise the literature and provide a summative assessment of the impact of narcolepsy on HRQoL. The aim of this review was to systematically review the literature assessing HRQoL in people with narcolepsy, provide pooled mean scores of the domains of the various HRQoL tools used in this population if possible, and to compare HRQoL in people with narcolepsy with general population norms and other chronic health conditions. Additional objectives of this review are to explore: (a) the heterogeneity of the published studies; (b) the tools used to assess HRQoL in this population; and (c) the influence of study characteristics on HRQoL.

2 | METHODS

This systematic review sought to identify the HRQoL of people with narcolepsy. This review followed the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statement guidelines. A study protocol that included the proposed search strategy and methodology was registered with PROSPERO, the international prospective registry of systematic reviews (PROSPERO) database (www.crd.york.ac.uk/prospero/) in April 2020 (Identification number: CRD42020156036).

2.1 | Eligibility criteria

The target population for this review was people with narcolepsy recruited from the general population, primary care or secondary care settings. Observational studies (case–control, cohort and cross-sectional) and experimental studies (randomised control trials, pre-post design, quasi-experimental) were deemed eligible if they assessed HRQoL in people with narcolepsy using a validated HRQoL questionnaire. HRQoL has been defined as "a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning; it has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life. However, more specifically HRQoL is a measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy" (Ahmed & Andrich, 2015). Articles were deemed ineligible for inclusion if they were case-series, case reports, expert opinion or consensus statements, or deduplicate studies that utilised the same participant data. Studies were required to provide mean scores with standard deviations (SDs) or standard errors (SEs) for each domain of their chosen HRQoL tool to be eligible for inclusion for each respective meta-analysis. Articles were restricted to those published in English; however, no limitation was placed on the publication year of articles.

2.2 | Data sources and search strategy

In collaboration with a senior medical librarian with specialist skills in systematic review searching (DM), a comprehensive search strategy was developed. The search encompassed four electronic databases: CINAHL, EMBASE, Medline (OVID) and Web of Science. The terms searched consisted of keywords and subject headings that were adapted for each database, and can be divided into three categories: (a) the condition (e.g. "narcolepsy", "narcolepsy type 1", "narcolepsy type 2", "narcolepsy with cataplexy"); (b) HRQoL ("quality of life", "quality of life assessment", "HRQoL"); and (c) HRQoL tools (e.g. "Short Form 36", "European Quality of Life 5 Dimensions Visual Analogue Scale", "functional outcome of sleep questionnaire"). The reference lists of articles identified in the initial search were scanned to identify any studies potentially missed.

2.3 | Selection of eligible studies

Articles were retrieved and deduplicated. Titles and abstracts were screened to determine their eligibility for inclusion by two researchers (RT and JB). Inter-rater disagreements were resolved through careful re-examination and discussion of the article between reviewers until a consensus was reached. The full texts of the potentially eligible studies were retrieved and independently assessed by both reviewers (RT and JB) to determine eligibility for inclusion in the final analyses. A similar method of addressing disagreements between researchers was applied for the full-text screening phase.

2.4 | Data extraction and quality assessment

Primary data extraction was conducted by RT, with JB examining the articles independently to reduce bias. Two researchers (RT and JB) independently appraised the risk of bias of included studies, with disagreements resolved through discussion between researchers until a conclusion was reached. A modified version of the Joanna Briggs Institute Checklist for Analytical Cross-Sectional Studies (Moola et al., 2017) was utilised to assess the risk of bias of included studies. This modified tool utilised the following five domains to assess bias: (a) sample; (b) subjects and setting; (c) objective measures of disease; (d) outcome measured; and (e) statistical analysis. Any discrepancies were resolved through discussion and review of the original article. If included articles were longitudinal or follow-up studies, baseline HRQoL data were selected for analysis.

2.5 | Statistical analysis

Statistical heterogeneity was determined using I^2-values, with values nearing 25%, 50% and 75% representing low, moderate and high heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003). As high levels of heterogeneity were identified between studies, random-effects meta-analyses with 95% confidence intervals (CIs) using Comprehensive Meta-Analysis were employed. Meta-analyses were conducted for each domain of the Short Form 36 (SF36), and the utility and visual analogue scale (VAS) scores of the EQ5D. Two separate meta-analyses were conducted for the physical (PCS) and mental (MCS) component summaries for the SF36, respectively. The first meta-analyses included only studies that provided calculated PCS and MCS values and their SDs. The second meta-analysis utilised the formula outlined by Taft, Karlsson, and Sullivan (2001) to calculate the PCS and MCS values from the domain scores when summary scores were not provided. SDs for these PCS and MCS scores were imputed according to the process outlined by Furukawa, Barbui, Cipriani, Brambilla, and Watanabe (2006). HRQoL questionnaires that were unable to be meta-analysed were discussed in a narrative summary. The impact of study variables and characteristics on HRQoL was assessed using Spearman's correlation analyses with adjusted r^2. The HRQoL of people with narcolepsy was compared against normative SF36 values obtained from the USA (Ware, Snow, Kosinski, & Gandek, 1993), UK (Jenkinson, Coulter, & Wright, 1993), France (Audureau, Rican, & Coste, 2013) and Norway (Ribu, Hanestad, Moum, Birkeland, & Rustoen, 2007). Data from people with narcolepsy were also plotted alongside data from people with epilepsy (Hermann et al., 1996), multiple sclerosis (Hermann et al., 1996), diabetes (Ribu et al., 2007) and hypertension (Kusek et al., 2002).

3 | RESULTS

3.1 | Study screening

The search strategy yielded 5,706 articles and, following deduplication, 3,399 unique articles had their titles and abstracts assessed for eligibility. From these articles, 3,338 articles were deemed ineligible and excluded. The full texts of the remaining 61 articles were screened to determine eligibility for inclusion, and 31 were excluded; with 24 being published abstracts, three duplicate data sets, three utilising ineligible outcome measures, and one study that assessed people without a formal diagnosis of narcolepsy. The remaining 30 articles were included in a descriptive synthesis, of which 17 articles were included in the SF36 meta-analysis, and five in the EQ5D meta-analysis. Figure 1 shows the study selection process.

3.2 | Characteristics of included studies

The characteristics of the included studies are outlined in Table 1. The 30 reviewed studies represent a total sample of 4,600 people with narcolepsy, of which 54.31% were female (n = 2,498). The number of

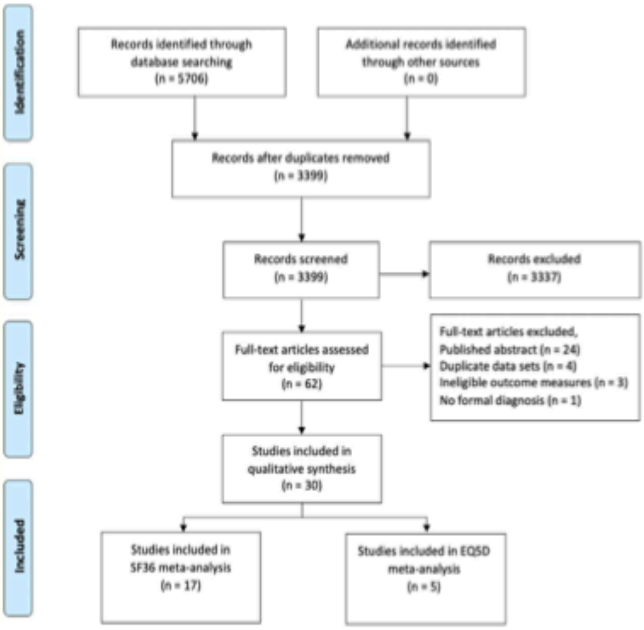

FIGURE 1 Flow diagram of studies screened for eligibility

TABLE 1 Study characteristics

Author	Year	Country	Study type	Industry funding	Sample size	M/F	Age (years)	Instrument	Quality Score	Comparison Groups/Control
Becker	2004	America	Cohort study	Yes	151	70/81	39.00 (18–68)	SF36	4/5	No control group
Beusterien	1999	America	RCT	NR	481	251/307	42	SF36 with additional scales	3/5	Placebo control
Bogan	2017	America	Post hoc analysis	Yes	228	79/149	40.50 (± 15.30)	SF-36	4/5	Placebo control
Campell	2011	New Zealand	Cross-sectional	No	54	20/34	54.70 (± 18.30)	SF36	3/5	No control group
Daniels	2001	UK	Cross-sectional	No	305	120/185	56.00 (18–89)	SF36	3/5	No control group
Dauvilliers	2009	France	Cross-sectional	Yes	492	238/254	41.64 (± 16.53)	SF36	5/5	No Control Group: Compared NT1, NT2 and IH
Dauvilliers	2011	France	Cross-sectional	Yes	67	31/36	44.8% < 40; 55.2% > 40	SF36, FOSQ	5/5	Compared with matched controls
Dauvilliers	2017	France	Cross-sectional	NR	175	104/71	41.50 (± 17.36)	EQ5D	4/5	Compared drug-free and treated patients
Dauvilliers	2019	France	Cross-sectional	NR	39	22/17	39.45 (± 18.20)	EQ5D	4/5	No control group: compared IH with NT1
David	2012	Portugal	Cross-sectional	NR	51	26/25	43.40 (± 15.30)	SF36	4/5	Compared with population norms
Dodel	2007	Germany	Cross-sectional	NR	75	46/29	48.90 (± 15.20)	SF36, EQ5D	4/5	Compared with population norms
Droogleever Fortuyn	2012	Netherlands	Cross-sectional	NR	80	46/34	48.3 (± 14.70)	SF36	3/5	No Control Group Compared fatigued versus non-fatigued
Emsellem	2020	America	RCT	Yes	231	82/154	36.23 (± 13.20)	SF36, EQ5D, FOSQ	4/5	Placebo control
Ervik	2006	Norway	Cross-sectional	NR	77	16/54	53.0 (± 17.40)	SF36	5/5	No control group
Flores	2016	America	Cross-sectional	Yes	437	219/218	46.70 (± 16.40)	SF36 PCS and MCS	3/5	Compared with population norms
Ingravallo	2008	Italy	Cross-sectional	No	15	9/6	48.70 (± 18.80)	SF36 PCS and MCS	5/5	No control group
Ingravallo	2012	Italy	Cross-sectional	NR	100	51/49	37.10 (18–65)	EQ5D	3/5	Compared with population norms
Kapella	2015	America	Cross-sectional	No	122	27/95	27.10 (± 5.00)	SF36, FOSQ	3/5	Acquaintance Approach for control group
Kayaba	2018	Japan	Cross-sectional	No	39	20/119	24.60 (± 8.30)	SF36 PCS and MCS	4/5	Compared with BIISS and DSPD
Kovalska	2016	Czech Republic	Case–control	No	42	18/24	71.86 (± 7.45)	VAS EQ5D	5/5	Age- and gender-matched controls
Mitler	2000	America	Cross-sectional	No	478	220/258	42.00 (± 13.0)	SF36	4/5	No control group
Ozaki	2008	Japan	Cross-sectional	No	55	20/35	30.29 (± 10.59)	SF36	5/5	Treated versus drug-naïve

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Study type	Industry funding	Sample size	M/F	Age (years)	Instrument	Quality Score	Comparison Groups/Control
Ozaki	2012	Japan	Cross-sectional	No	131	71/63	32.21 (± 8.68)	SF36	5/5	Treated versus drug-naïve
Rovere	2008	Brazil	Cross-sectional	No	40	12/28	41.85 (± 14.5)	WHOQOL-BREF	3/5	Control group present
Sarkanen	2016	Finland	Cross-sectional	NR	51	25/26	NR	WHO-5 Well-Being Index	4/5	Compared with NT1
Song	2019	South Korea	Cross-sectional	No	63	43/20	27.03 (± 9.29)	K-SF36	5/5	No control group
Teixeira	2004	Scotland	Cross-sectional	No	49	30/19	47.00 (± 18.00)	SF36, FOSQ	5/5	Untreated OSAHS and CPAP-treated OSAHS
Vignatelli	2004	Italy	Cross-sectional	No	108	62/46	43.20 (± 16.40)	SF36	5/5	Compared with population norms
Vignatelli	2011	Italy	5-year prospective cohort	No	54	42/12	48.00 (± 18.40)	SF36	5/5	5-year follow-up
Weaver	2006	America	RCT	Yes	228	79/149	40.50 (± 15.30)	FOSQ	5/5	Placebo control

BISS, behaviourally induced insufficient sleep syndrome; CPAP, continuous positive airway pressure; DSPD, delayed sleep phase disorder; FOSQ, Functional Outcome of Sleep Questionnaire; IH, idiopathic hypersomnia; K-SF36, Korean Short Form 36; MCS, mental component summary; NR, not reported; NT1, type 1 narcolepsy; NT2, type 2 narcolepsy; OSAHS, obstructive sleep apnea hypopnea syndrome; PCS, physical component summary; RCT, randomised controlled trial; SF36, Short Form 36; VAS, visual analogue scale.

participants in each study ranged from 15 to 558, with a mean of 153 participants in the included studies. The mean age of all participants was 40.8 years, with a 95% CI ranging from 37.12 to 44.46 years. The 30 included studies originated from 13 different countries (Table 1). Studies were predominantly based in North America and Europe (80.00%), and approximately one-third of studies (*n* = 8) were published in the USA (Becker, Schwartz, Feldman, & Hughes, 2004; Beusterien et al., 1999; Bogan et al., 2017; Emsellem et al., 2020; Flores et al., 2016; Kapella et al., 2015; Mitler, Harsh, Hirshkowitz, & Guilleminault, 2000; Weaver & Cuellar, 2006). Four studies were published in France (Dauvilliers et al., ,2009, 2011, 2017, 2019) and Italy (Ingravallo et al., ,2008, 2012; Vignatelli et al., 2004; Vignatelli, Plazzi, Peschechera, Delaj, & D'Alessandro, 2011), respectively. Additionally, three studies were published in Japan (Kayaba, Sasai -Sakuma, & Inoue, 2018; Ozaki et al., ,2008, 2012). One study was published from each of the remaining countries (Table 1).

3.3 | HRQoL measurement tools

A total of seven different questionnaires (SF8, SF12, SF36, EQ5D, WHOQOL-BREF, WHO-5, Functional Outcomes of Sleep Questionnaire [FOSQ]) were utilised in the 30 included studies to assess HRQoL in this population. Of these questionnaires, six of these were generic, and one was a sleep-specific HRQoL questionnaire (Table 2). The most frequently used questionnaire was the SF36, which was utilised in 22 of the 30 studies (Table 1). The EQ5D was used to assess HRQoL in six studies (Dauvilliers et al., 2017, 2019; Dodel et al., 2007; Emsellem et al., 2020; Ingravallo et al., 2012; Kovalska et al., 2016), and the FOSQ was used in five studies (Dauvilliers et al., 2011; Emsellem et al., 2020; Kapella et al., 2015; Teixeira, Faccenda, & Douglas, 2004; Weaver & Cuellar, 2006). The remaining questionnaires were used in singular studies (Table 1).

3.4 | Study designs

A total of 22 studies utilised a cross-sectional design to assess HRQoL (Table 1), making it the most commonly used method to assess HRQoL in this population. Studies by Weaver and Cuellar (2006), Beusterien et al. (1999) and Emsellem et al. (2020) utilised multicentre, randomised, placebo-controlled designs for their studies. Cohort studies were conducted by Becker et al. (2004), and Vignatelli, Plazzi, Peschechera, Delaj, and D'Alessandro (2011). The latter study was the only study that incorporated a longitudinal design in this population, as it followed up with participants 5 years after the initial study conducted by Vignatelli et al. (2004). The remaining study designs were only used in individual studies, and are shown in Table 1.

3.5 | Employment status

Nine of the included studies, representing a sample of 643 participants, reported the employment status of respondents (David et al.,

TABLE 2 Meta-analysed SF36 results and associated study variables

	PF	RP	BP	GH	PCS	PCSI	V	SF	RE	MH	MCS	MCSI
Pooled mean	67.84	45.99	64.19	53.59	48.32	45.91	42.01	55.66	55.22	58.71	45.47	42.98
95% CI	59.26–76.42	40.80–51.17	56.87–71.50	48.12–59.05	44.45–52.20	43.01–48.81	37.22–46.79	46.56–64.75	48.79–61.66	52.14–65.27	39.97–50.97	39.02–46.95
Heterogeneity I^2%	99.58	95.76	98.87	98.19	99.10	98.89	98.15	99.15	97.41	98.83	99.43	99.11
Correlators												
Sample size	−0.217	−0.566	−0.154	0.091	−0.310	0.132	−0.434	−0.273	−0.119	**1.000****	−0.600	−0.288
Mean age	**0.608***	**0.643***	**0.671***	0.245	−0.168	0.195	0.392	**0.811****	**0.706***	−0.497	−0.119	0.436
% Female	−0.448	0.021	−0.203	−0.503	−0.466	−0.327	−0.238	−0.203	−0.385	0.028	−0.285	−0.395
Publication year	**−0.748****	0.035	**−0.638***	**−0.0723****	0.000	−0.210	0.007	**−0.603***	−0.473	−0.063	−0.142	0.330

BP, Bodily Pain; CI, confidence interval; GH, general health; MCS, mental component summary; MCSI, mental component summary (imputed standard deviations); MH, mental health; PCS, physical component summary; PCSI, physical component summary (imputed standard deviations); PF, physical functioning; RE, emotional role limitations; RP, physical role limitations; SF, social functioning; V, vitality.

*Correlation is significant at p = .05.; **Correlation is significant at p = .01.

2012); Dodel et al., 2007; Ingravallo et al., 2008, 2012; Kapella et al., 2015; Ozaki et al., 2008, 2012; Rovere, Rossini, & Reimão, 2008; Vignatelli et al., 2004). Of those surveyed, 69.92% (n = 450) reported being employed.

Five studies reported employment-related difficulties experienced by respondents (Flores et al., 2016; Ingravallo et al., 2012; Kapella et al., 2015; Kovalska et al., 2016; Teixeira et al., 2004). Changes of employment were reported by the working population of the sample recruited by Ingravallo et al. (2012) (n = 84), with 31% (n = 26) reporting changes to work due to narcolepsy, 58% (n = 15) changing job types, 31% (n = 8) losing or leaving their jobs without finding other employment, and 11% (n = 3) changing their working schedule.

Termination from employment was frequently reported, with 33% (n = 40) of those surveyed by Kapella et al. (2015) reporting being previously discharged from employment, and 52% (n = 25) of respondents recruited by Teixeira et al. (2004) reporting losing or leaving a job. As reported by Kovalska et al. (2016), participants with narcolepsy changed employment more frequently than age-and-gender-matched controls (2.67 ± 2.45 times versus 2.42 ± 1.83 times, respectively).

Participants surveyed by Teixeira et al. (2004) reported work-related difficulties such as falling asleep at work (67%, n = 39), low productivity (37%, n = 18) and accidents at work (15%, n = 7). The economic consequences of narcolepsy on employment were quantified by Flores et al. (2016), and compared with matched controls, people with narcolepsy had significantly higher costs associated with absenteeism ($12,839 versus $7,631) and presenteeism ($7,013 versus $4,987).

3.6 | Impact on HRQoL as measured by the SF36

The pooled mean results of the SF36 domains are reported with 95% CIs in Table 2. From the obtained results, the mental domains of the quality of life in people with narcolepsy are more affected than the physical domains. Both the imputed (42.98) and non-imputed (45.87) MCS were lower than the imputed (45.91) and non-imputed (49.32) PCS (Table 2). The most affected SF36 domains were Vitality (42.01) and Physical Role Limitations (45.99), and the least affected domains were Physical Functioning (67.84) and Bodily Pain (64.19; Table 2).

3.6.1 | Associated study variables

Spearman's correlation analyses with adjusted r^2-values were used to assess the factors associated with HRQoL, and included study quality, sample size, publication year, the proportion of female participants, and mean participant age (Table 2). Participant age was shown to significantly positively correlate with physical functioning (r^2 = .608, p = .05), physical role limitations (r^2 = .643, p = .05), bodily pain (r^2 = .651, p =.05), emotional role limitations (r^2 = .706, p = .05) and social functioning (r^2 = .811, p = .01). Similarly, publication year demonstrated significant negative correlations with physical functioning (r^2 = −.748, p = .01), general health (r^2 = .0723, p = .01) and social functioning ($r^2 = -.603$, $p = .05$). This finding implies that reported HRQoL has improved throughout the years. Sample size was shown to have a strong positive correlation on the mental health domain ($r^2 = 1.000$, $p = .01$; Table 2).

3.6.2 | Comparison of HRQoL with general population norms and other chronic health conditions

The mean HRQoL for each domain of the SF36 was plotted against the general population norms for the USA (Ware et al., 1993), UK (Jenkinson et al., 1993), France (Audureau et al., 2013) and Norway (Ribu et al., 2007) in Figure 2. This comparison indicates that the HRQoL of people with narcolepsy is considerably impaired when compared with the general population, particularly the physical role limitations, social functioning, and emotional role limitations domains. Figure 3 compares the SF36 scores of people with narcolepsy with other chronic health conditions, including epilepsy (Hermann et al., 1996), multiple sclerosis (Hermann et al., 1996), diabetes (Ribu et al., 2007) and hypertension (Kusek et al., 2002). People with narcolepsy experience consistently lower levels of mental health, emotional role limitations, social functioning and

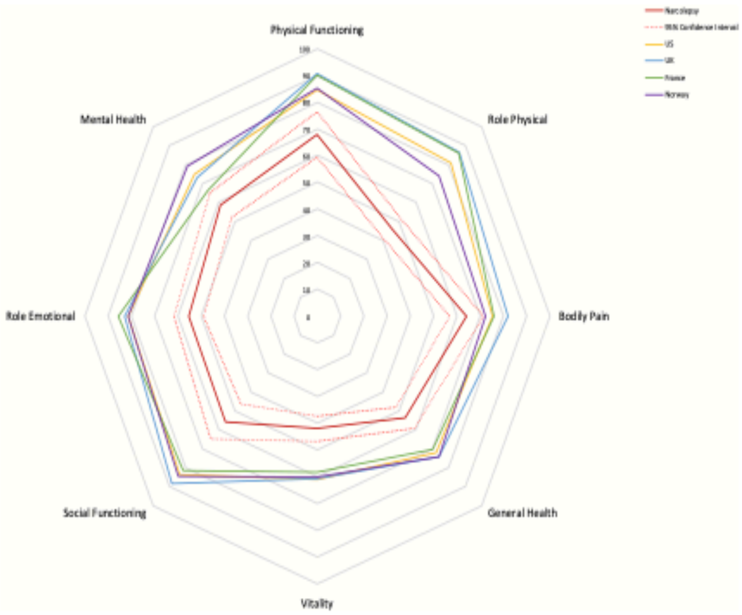

FIGURE 2 Short Form 36 (SF36) values compared with general population norms

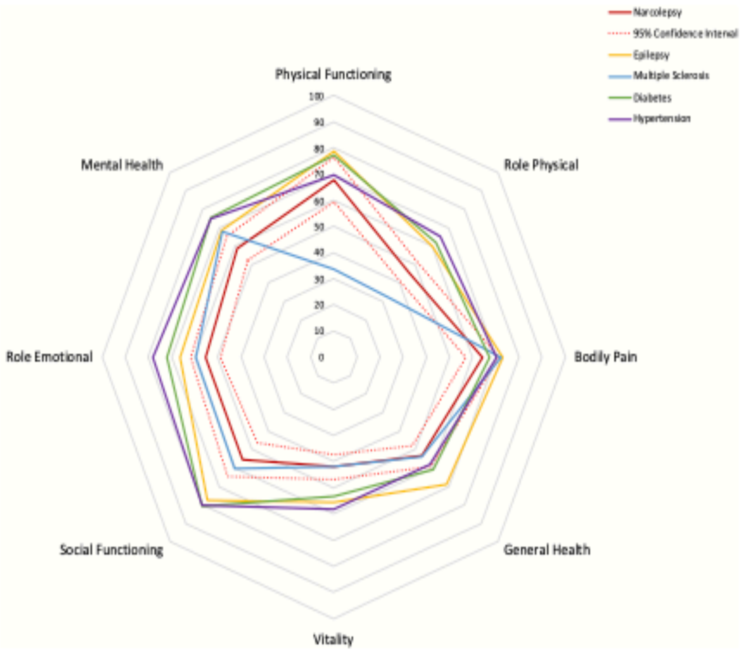

FIGURE 3 Short Form 36 (SF36) values compared with chronic diseases

bodily pain when compared with the aforementioned chronic health conditions. When compared with epilepsy, diabetes and hypertension, people with narcolepsy scored lower in all eight domains of the SF36. With the exception of physical functioning, physical role limitations and vitality, people with narcolepsy scored lower than people with multiple sclerosis in the remaining five SF36 subscales (Figure 3).

3.7 | Other HRQoL questionnaires

3.7.1 | EQ5D

The EQ5D was utilised in six studies (Dauvilliers et al., 2017, 2019; Dodel et al., 2007; Emsellem et al., 2020; Ingravallo et al., 2012; Kovalska et al., 2016) to assess HRQoL in people with narcolepsy. The mean utility score obtained from the analysed studies was 0.85 (0.82–0.88, 95% CI). Additionally, the mean score obtained from the VAS of the EQ5D was 66.63, with the 95% CI ranging from 61.83 to 71.43. Figure 4 compares the VAS scores of the sample with narcolepsy with population norms of the USA, UK and France (Szende, Janssen, & Cabases, 2014).

3.8 | FOSQ

The FOSQ was utilised in five studies (Dauvilliers et al., 2011; Emsellem et al., 2020; Kapella et al., 2015; Teixeira et al., 2004; Weaver & Cuellar, 2006) to assess HRQoL in this population. Studies by Dauvilliers et al. (2011) and Weaver and Cuellar (2006) were excluded from the analysis as they failed to report their baseline values for the FOSQ domains. The results from Kapella et al. (2015) and Teixeira et al. (2004) identified that Activity Levels (2.27) and Vigilance (2.34) were the most affected quality of life domains, and Sexual Wellbeing (3.0) and Social Outcomes (2.71) were the least affected domains. The total score obtained from Kapella et al. (2015) (13.3) was considerably higher than that of Teixeira et al. (2004) (9.5). However, the study by Teixeira et al. (2004) did not assess Sexual Wellbeing. When the Sexual Wellbeing domain is excluded from the results obtained by Kapella et al. (2015), their adjusted total score becomes 10.3. The FOSQ-10, a concise version of the FOSQ, was utilised by Emsellem et al. (2020). The total scores for the FOSQ-10 ranged from 11.4 to 12.2, with a mean total score of 11.675 (3.21) reported.

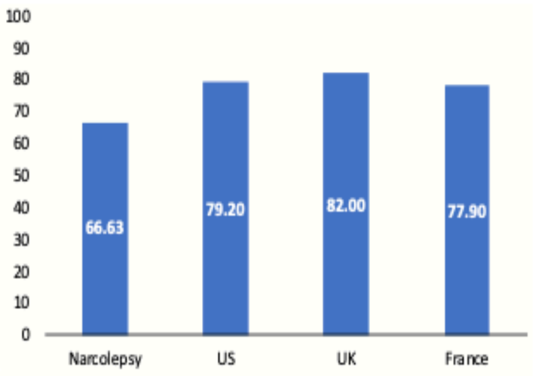

FIGURE 4 EQ5D visual analogue scale (VAS) scores compared with general population norms

3.8.1 | Concise short forms

The SF8 and SF12 were utilised by Kayaba et al. (2018) and Flores et al. (2016), respectively. The study by Flores et al. (2016) failed to report the SF12 results obtained by their study. The study by Kayaba et al. (2018) reported the component summaries obtained by their participants, and identified that physical wellbeing (50.7 ± 6.4) was less severely affected than mental wellbeing (44.8 ± 9.6), as measured by the PCS and MCS, respectively.

3.8.2 | WHO questionnaires

The WHOQOL-BREF and WHO-5 were used by Rovere et al. (2008) and Sarkanen, Alakuijala, and Partinen (2016) to assess HRQoL in their studies, respectively. The results obtained by Rovere et al. (2008) identified that Physical Wellbeing was the most affected HRQoL domain (48.93 ± 15.67), followed by Environmental factors (50.16 ± 15.32). Conversely, Social Wellbeing (60.83 ± 17.11) and Psychological Wellbeing (56.04 ± 14.74) were the least affected HRQoL domains in this population. The results obtained from Sarkanen et al. (2016) failed to report baseline values for the WHO-5, only reporting the total scores obtained upon the initial (45.5 ± 24.8) and follow-up visits (48.0 ± 19.3).

3.9 | Quality assessment

Quality assessment of the included studies can be found in Table 3. The appraisal scores for the included studies ranged from 3 to 5, with articles successfully providing sufficient information for a mean of 4 (± 0.82) of the five domains. Only 12 studies scored the maximal possible score of 5, and 10 scored 4/5. Inclusion criteria were the poorest performing section, with 13 of the 30 articles failing to clearly state the inclusion criteria for their study (Table 3).

4 | DISCUSSION

This was the first systematic review and meta-analyses to comprehensively assess the impact of narcolepsy on HRQoL. This review identified that narcolepsy negatively impacts HRQoL, and that people with narcolepsy report considerably lower quality of life than general populations as well as several other chronic disease populations. Furthermore, the majority of included studies were of

TABLE 3 Quality appraisal using the JBI checklist for analytical cross-sectional studies

Study ID	Inclusion criteria	Subjects and setting	Objective measures disease	Outcomes measures	Statistical analysis
Becker et al. (2004)	Yes	Unclear	Yes	Yes	Yes
Beusterien et al. (1999)	Unclear	Unclear	Yes	Yes	Yes
Bogan et al. (2017)	Yes	Unclear	Yes	Yes	Yes
Campbell et al. (2011)	Unclear	Yes	No	Yes	Yes
Daniels et al. (2001)	Unclear	Yes	Unclear	Yes	Yes
Dauvilliers et al. (2009)	Yes	Yes	Yes	Yes	Yes
Dauvilliers et al. (2011)	Unclear	Yes	Yes	Yes	Yes
Dauvilliers et al. (2017)	Unclear	Yes	Yes	Yes	Yes
Dauvilliers et al. (2019)	Yes	Yes	Yes	Yes	Yes
David et al. (2012)	Unclear	Yes	Yes	Yes	Yes
Dodel et al. (2007)	Unclear	Yes	Yes	Yes	Yes
Droogleever Fortuyn et al. (2012)	Unclear	Unclear	Yes	Yes	Yes
Emsellem et al. (2020)	Yes	Unclear	Yes	Yes	Yes
Ervik et al. (2006)	Yes	Yes	Yes	Yes	Yes
Flores et al. (2016)	Yes	Unclear	No	Yes	Yes
Ingravallo et al. (2008)	No	Unclear	Yes	Yes	Yes
Ingravallo et al. (2012)	Yes	Yes	Yes	Yes	Yes
Kapella et al. (2015)	Unclear	Yes	Unclear	Yes	Yes
Kayaba et al. (2018)	Unclear	Yes	Yes	Yes	Yes
Kovalska et al. (2016)	Yes	Yes	Yes	Yes	Yes
Mitler et al. (2000)	Yes	Unclear	Yes	Yes	Yes
Ozaki et al. (2008)	Yes	Yes	Yes	Yes	Yes
Ozaki et al. (2012)	Yes	Yes	Yes	Yes	Yes
Rovere et al. (2008)	Unclear	Unclear	Yes	Yes	Yes
Sarkanen et al. (2016)	Unclear	Yes	Yes	Yes	Yes
Song et al. (2019)	Yes	Yes	Yes	Yes	Yes
Teixera et al. (2004)	Yes	Yes	Yes	Yes	Yes
Vignatelli et al. (2004)	Yes	Yes	Yes	Yes	Yes
Vignatelli et al. (2011)	Yes	Yes	Yes	Yes	Yes
Weaver & Cuellar (2006)	Yes	Yes	Yes	Yes	Yes

high quality as measured by the JBI Checklist for Analytical Cross-Sectional Studies tool.

The most notably affected HRQoL domain compared with the general population was physical role limitations. However, mental domains were also considerably affected; in particular, social functioning and emotional role limitations. Furthermore, people with narcolepsy reported considerably lower HRQoL in all SF36 domains compared with people with diabetes, epilepsy and hypertension. When compared with multiple sclerosis, with the exception of physical functioning (+34.34), physical role limitations (+13.29) and vitality (+0.11), people with narcolepsy scored lower than in the remaining five SF36 subscales. These comparisons serve to highlight the high symptom burden associated with narcolepsy. The finding that people with narcolepsy report poorer quality of life than people with epilepsy is consistent with the findings of the study conducted by Broughton, Guberman, and Roberts (1984). The comparison between narcolepsy and epilepsy is particularly notable as both neurological conditions cause individuals to experience episodic attacks and excessive daytime sleepiness to some extent. However, EDS in people with narcolepsy is a consistent feature as part of their underlying condition, whilst EDS in people with epilepsy may be as a result of medications, uncontrolled seizures or a comorbid sleep disorder (Broughton et al., 1984). More appropriate comparisons are limited until similar reviews are conducted in other disorders of hypersomnolence.

This review shows the burden that narcolepsy places on people experiencing this condition. In particular, the MCS scores (42.98) were lower than those of the PCS (45.91), suggesting that narcolepsy has a more significant impact on the mental wellbeing than the physical wellbeing of people with narcolepsy. However, the most affected HRQoL domains primarily related to physical wellbeing, as physical role limitations (45.99) and vitality (42.01), were the most affected SF36 domains, and activity levels (2.27) were the most affected FOSQ domain. These results highlight that impairment with daily activities, fatigue and reduced energy levels are central to the lived experience associated with narcolepsy. A possible explanation for this finding is the interrelationship between physical performance and mental wellbeing in people with narcolepsy suggested by Morse and Sanjeev (2018), with less physical activity in people with narcolepsy being linked to poorer mood (Bruck, Kennedy, Cooper, & Apel, 2005). This population generally has reduced opportunities to exercise due to time constraints related to sleepiness and social isolation (Kapella et al., 2015), and considerably lower physical activity has been reported in people with narcolepsy compared with the general population (Parmar et al., 2019). A vicious cycle can be established with sedentary behaviour promoting increased sleepiness severity (Golden & Lipford, 2018), and this increased symptom burden further reducing habitual levels of physical activity and HRQoL (Matoulek, Tuka, Fialova, Nevsimalova, & Sonka, 2017). The impact of physical activity levels on physical and mental wellbeing in this population warrants further exploration.

This review identified significant negative correlations between date of publication and the physical functioning (p = .01), general health (p = .01) and social functioning (p = .05) domains of the SF36. This finding may imply that improved treatment options and knowledge about narcolepsy by medical professionals can have positive effects on HRQoL in people with narcolepsy. Similarly, this review identified that older age of symptom onset was negatively associated with physical role limitations, physical functioning and vitality (p = .01). In a study by Ingravallo et al. (2012), people with the onset of narcolepsy occurring later in life viewed their health as worse, achieved lower educational levels and experienced more employment problems than those with onset earlier in life. Possible explanations for the relationship between later onset and poorer HRQoL may include reduced habituation to their condition. The effect of ageing on HRQoL, however, remains ambiguous. Increasing age was found to be positively associated with physical functioning, physical role limitations, bodily pain, emotional role limitations (p = .05) and social functioning (p = .01). However, the findings from studies by Vignatelli et al. (2004) and Vignatelli, Plazzi, Peschechera, Delaj, and D'Alessandro (2011) showed that there was no significant difference in SF36 domain scores, and only slight declines in the component summaries. A possible explanation for the positive correlation associated with age is that as this population ages, they become more accepting of their condition. Further longitudinal research is necessary to evaluate the long-term impact of ageing on HRQoL in this population.

This review highlighted that there was diversity in HRQoL tools utilised, with a total of six tools employed. However, there was some agreement on the tools used to measure HRQoL in people with narcolepsy as over two-thirds of the included studies utilised the SF36 (n = 22). Only five studies utilised the FOSQ, a sleep-disorder-specific tool and, of which, four utilised a combination of generic and sleep-disorder-specific tools. Although the SF36 is a comprehensive generic HRQoL tool, it may lack the specificity to assess the subtle aspects of the HRQoL imposed by narcolepsy. Similarly, although the FOSQ may be a sleep-disorder-specific tool, it is not a narcolepsy-specific tool and similar issues to the SF36 may arise. The study by Beusterien et al. (1999) reported that they utilised supplemental scales in an attempt to assess common issues in narcolepsy, namely measures of overall health perceptions, driving limitations and social support. To the authors' knowledge, this was the only study to incorporate these additional scales to assess HRQoL in people with narcolepsy. This review has identified the considerable need for the development of a psychometrically robust narcolepsy-specific tool to assess HRQoL in this population. The combination of a generic and a condition-specific HRQoL tool is recommended to assess HRQoL in this population, as this would enable comparison with other health conditions, and detection of sleep-disorder-specific HRQoL impairments.

Several limitations pertained to this review. Firstly, this review excluded articles that were not published in English or grey literature due to time constraints. The decision to include the baseline values obtained from randomised control trials may have limited this review, as the obtained sample may not be wholly representative of people with narcolepsy due to the strict inclusion criteria that are often associated with such trials. Additionally, participants would likely have been on different medication regimens and, as a result, the heterogeneity of the overall sample must be considered when interpreting the results of this review. Furthermore, the certainty of participants' diagnosis of narcolepsy must be considered, particularly for earlier studies, as their large and heterogenous samples may have included individuals with similar conditions such as insufficient sleep syndrome or idiopathic hypersomnia. Another potential limitation of this review was the substantial number of included studies that failed to report the PCS and MCS scores for the SF36 (n = 8). Although these summary scores could be calculated from the domain scores provided, the standard deviation of these scores could not be calculated and, as a result, standard deviations had to be imputed according to the formula described by Furukawa et al. (2006). Comparable methods were adopted by similar systematic reviews, such as the reviews conducted by Matcham et al. (2014) and Gu et al. (2019). Additionally, both the imputed and non-imputed values of the component summaries were reported to address this limitation. Another possible limitation of this study included the relatively small sample sizes of the chronic conditions used to compare against the SF36 domain scores obtained by people with narcolepsy. Consequently, the results of this comparison must be cautiously interpreted. As the majority of studies (n = 26) did not provide subgroup results, the comparison between type 1 and type 2 narcolepsy was unable to be made. Similarly, the relationship between employment status and HRQoL could not be explored as the nine studies that reported employment status used different tools. Strengths of this review include that PRISMA guidelines were closely followed to ensure that our search strategy captured the complete and relevant published literature. Furthermore, studies were evaluated using a standardised measure, and included studies were generally high quality as measured by the JBI tool.

5 | CONCLUSION

This is the first review that has attempted to systematically assess the impact of narcolepsy on HRQoL. HRQoL is an important endpoint in narcolepsy research. Given the reduced HRQoL in people with narcolepsy, its measurement can aid the assessment of treatment response, and can help guide the allocation of resources within the clinical setting. The results of this review demonstrated that people with narcolepsy experience substantial impairment of their mental and physical wellbeing compared with general populations as well as other chronic disease populations, but a more consistent approach is needed to explore the effect of narcolepsy on HRQoL. The possible usefulness of a validated, patient-reported measure specific for narcolepsy and its symptoms should be evaluated to measure the true impact of this disease. Future research should explore the effects of ageing on HRQoL in people with narcolepsy, HRQoL differences in NT1 and NT2, predictors of HRQoL, and the potential role of physical activity as well as other non-pharmacological strategies to improve mental and physical wellbeing in this population.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Ragy Tadrous: Protocol development, screening, data extraction, risk of bias assessment, data analysis and write up. Deirdre O'Rourke: Reviewing and editing completed manuscript. David Mockler: Creation of search strategy for database searching. Julie Broderick: Protocol development, screening, risk of bias assessment, reviewing and editing the completed manuscript.

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How to cite this article: Tadrous R, O'Rourke D, Mockler D, Broderick J. Health-related quality of life in narcolepsy: A systematic review and meta-analysis. *J Sleep Res*. 2021;00:e13383. https://doi.org/10.1111/jsr.13383

Appendix III: Systematic Review Search Strategy

EMBASE

1. 'narcolepsy'/exp OR 'hypersomnolence'/exp OR 'narcolepsy type 1'/exp OR 'narcolepsy type 2'/exp OR 'narcolepsy with cataplexy'/exp OR 'hypersomnia'/exp
2. (Narcolep* OR ‘sleep epilepsy’ OR ‘gelineau disease’ OR ‘gelineau syndrome’ OR ‘paroxysmal sleep’ OR hypersomn* OR Dyssomnia* OR 'narcolepsy with cataplexy' OR Narcolepsy-Cataplexy):ti,ab
3. #1 OR #2
4. 'quality of life'/exp OR 'quality of life assessment'/exp
5. (‘quality of life’ OR HRQL OR ‘life quality’):ti,ab
6. #4 OR #5
7. 'Short Form 36'/de OR 'Short Form 12'/de OR 'European Quality of Life 5 Dimensions Visual Analogue Scale'/exp OR 'sleep disorder assessment'/exp OR 'functional outcome of sleep questionnaire'/exp OR 'multiple sleep latency test'/exp
8. (‘Italian questionnaire on cataplexy’ OR ‘psychosocial aspects questionnaire’ OR ‘ullanlinna narcolepsy scale’ OR ‘Short Form 36' OR 'Short Form 12' OR 'European Quality of Life 5 Dimensions Visual Analogue Scale' OR ‘Epworth sleepiness scale’ OR ‘Stanford sleepiness scale’ OR ‘Insomnia Severity Index’ OR ‘Leeds Sleep Evaluation Questionnaire’ OR ‘functional outcome of sleep questionnaire’ OR ‘Pittsburgh Sleep Quality Index’ OR 'multiple sleep latency test'):ti,ab
9. #7 OR #8
10. #6 OR #9
11. #10 AND #3
12. 'conference abstract':it OR 'conference review':it
13. #11 NOT #12

Medline (OVID)

1. exp Narcolepsy/ OR Disorders of Excessive Somnolence/ OR Hypersomnolence, Idiopathic/
2. (Narcolep* OR sleep epilepsy OR gelineau disease OR gelineau syndrome OR paroxysmal sleep OR hypersomn* OR Dyssomnia* OR narcolepsy with cataplexy OR Narcolepsy-Cataplexy).ti,ab.
3. or/1-2
4. quality of life/
5. (quality of life OR HRQL OR life quality).ti,ab.
6. or/4-5
7. (Italian questionnaire on cataplexy OR psychosocial aspects questionnaire OR ullanlinna narcolepsy scale OR Short Form 36 OR Short Form 12 OR European Quality of Life 5 Dimensions Visual Analogue Scale OR Epworth sleepiness scale OR Stanford sleepiness scale OR Insomnia Severity Index OR Leeds Sleep

Evaluation Questionnaire OR functional outcome of sleep questionnaire OR Pittsburgh Sleep Quality Index OR multiple sleep latency test).ti,ab.

8. or/6-7
9. and/3,8

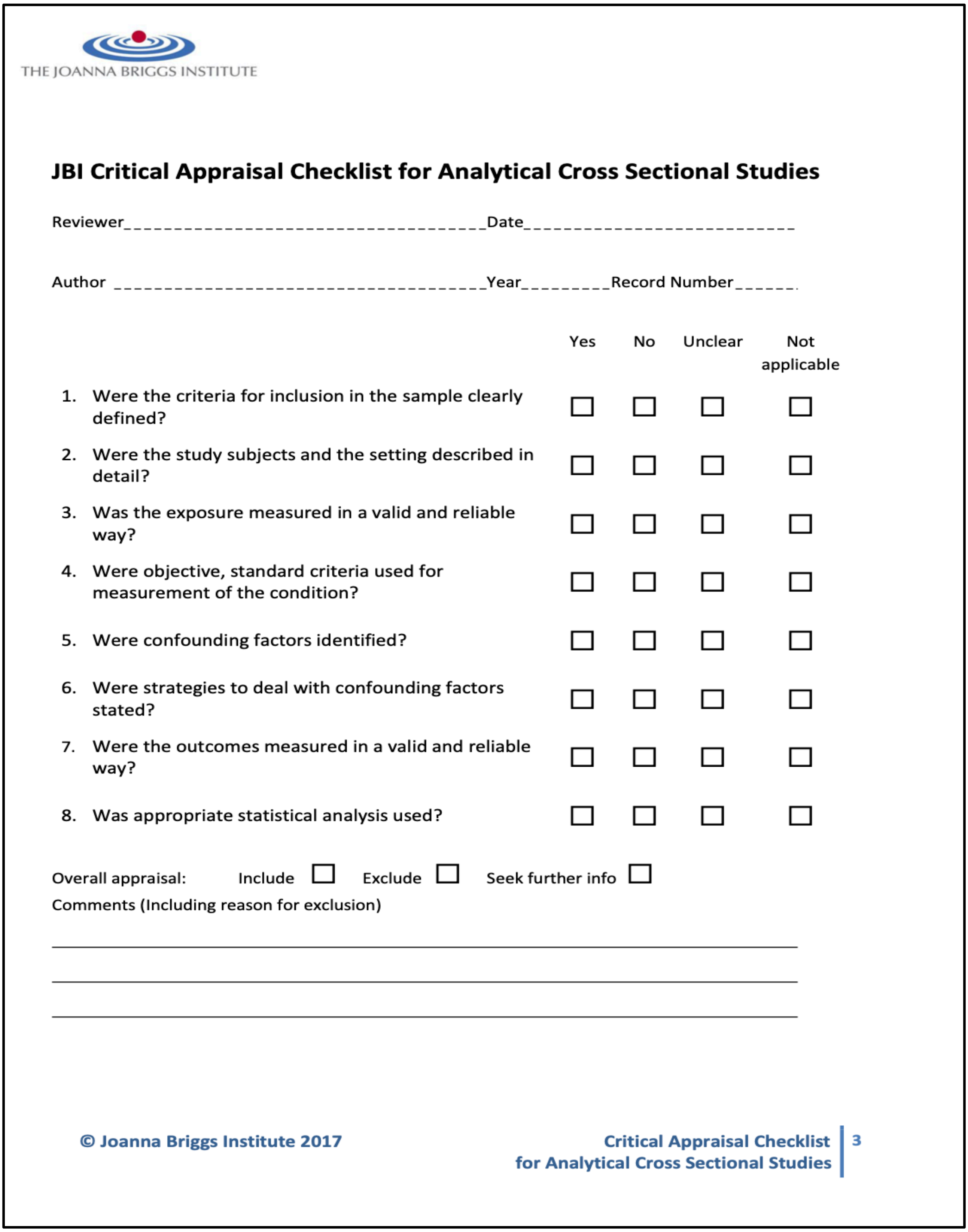
Web of Science
TS = ((Narcolep* OR “sleep epilepsy” OR “gelineau disease” OR “gelineau syndrome” OR “paroxysmal sleep” OR hypersomn* OR Dyssomnia* OR “narcolepsy with cataplexy”) AND ((“quality of life” OR HRQL OR “life quality”) OR (“Italian questionnaire on cataplexy” OR “psychosocial aspects questionnaire” OR “ullanlinna narcolepsy scale” OR “Short Form 36” OR “Short Form 12” OR “European Quality of Life 5 Dimensions Visual Analogue Scale” OR “Epworth sleepiness scale” OR “Stanford sleepiness scale” OR “Insomnia Severity Index” OR “Leeds Sleep Evaluation Questionnaire” OR “functional outcome of sleep questionnaire” OR “Pittsburgh Sleep Quality Index” OR “multiple sleep latency test”)))

CINAHL

1. (MH "Narcolepsy") OR (MH "Disorders of Excessive Somnolence")
2. TI (Narcolep* OR “sleep epilepsy” OR “gelineau disease” OR “gelineau syndrome” OR “paroxysmal sleep” OR hypersomn* OR Dyssomnia* OR “narcolepsy with cataplexy” OR Narcolepsy-Cataplexy) OR AB (Narcolep* OR “sleep epilepsy” OR “gelineau disease” OR “gelineau syndrome” OR “paroxysmal sleep” OR hypersomn* OR Dyssomnia* OR “narcolepsy with cataplexy” OR Narcolepsy-Cataplexy)
3. S1 OR S2
4. (MH "Quality of Life")
5. TI (“quality of life” OR HRQL OR “life quality”) OR AB (“quality of life” OR HRQL OR “life quality”)
6. S4 OR S5
7. TI (“Italian questionnaire on cataplexy” OR “psychosocial aspects questionnaire” OR “ullanlinna narcolepsy scale” OR “Short Form 36” OR “Short Form 12” OR “European Quality of Life 5 Dimensions Visual Analogue Scale” OR “Epworth sleepiness scale” OR “Stanford sleepiness scale” OR “Insomnia Severity Index” OR “Leeds Sleep Evaluation Questionnaire” OR “functional outcome of sleep questionnaire” OR “Pittsburgh Sleep Quality Index” OR “multiple sleep latency test”) OR AB (“Italian questionnaire on cataplexy” OR “psychosocial aspects questionnaire” OR “ullanlinna narcolepsy scale” OR “Short Form 36” OR “Short Form 12” OR “European Quality of Life 5 Dimensions Visual Analogue Scale” OR “Epworth sleepiness scale” OR “Stanford sleepiness scale” OR “Insomnia Severity Index” OR “Leeds Sleep Evaluation Questionnaire” OR “functional outcome of sleep questionnaire” OR “Pittsburgh Sleep Quality Index” OR “multiple sleep latency test”)
8. S6 OR S7
9. S3 AND S8

Results from all database searches 02/10/19 = 5706
After deduplication = 3503

Appendix IV: Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies



THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer______________________________________Date_____________________________

Author ______________________________________Year_________Record Number______

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

____

____

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Critical Appraisal Checklist for Analytical Cross Sectional Studies | 3

THE JOANNA BRIGGS INSTITUTE

Explanation of analytical cross sectional studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual.* The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Analytical cross sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. **Were the criteria for inclusion in the sample clearly defined?**

   The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. **Were the study subjects and the setting described in detail?**

   The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

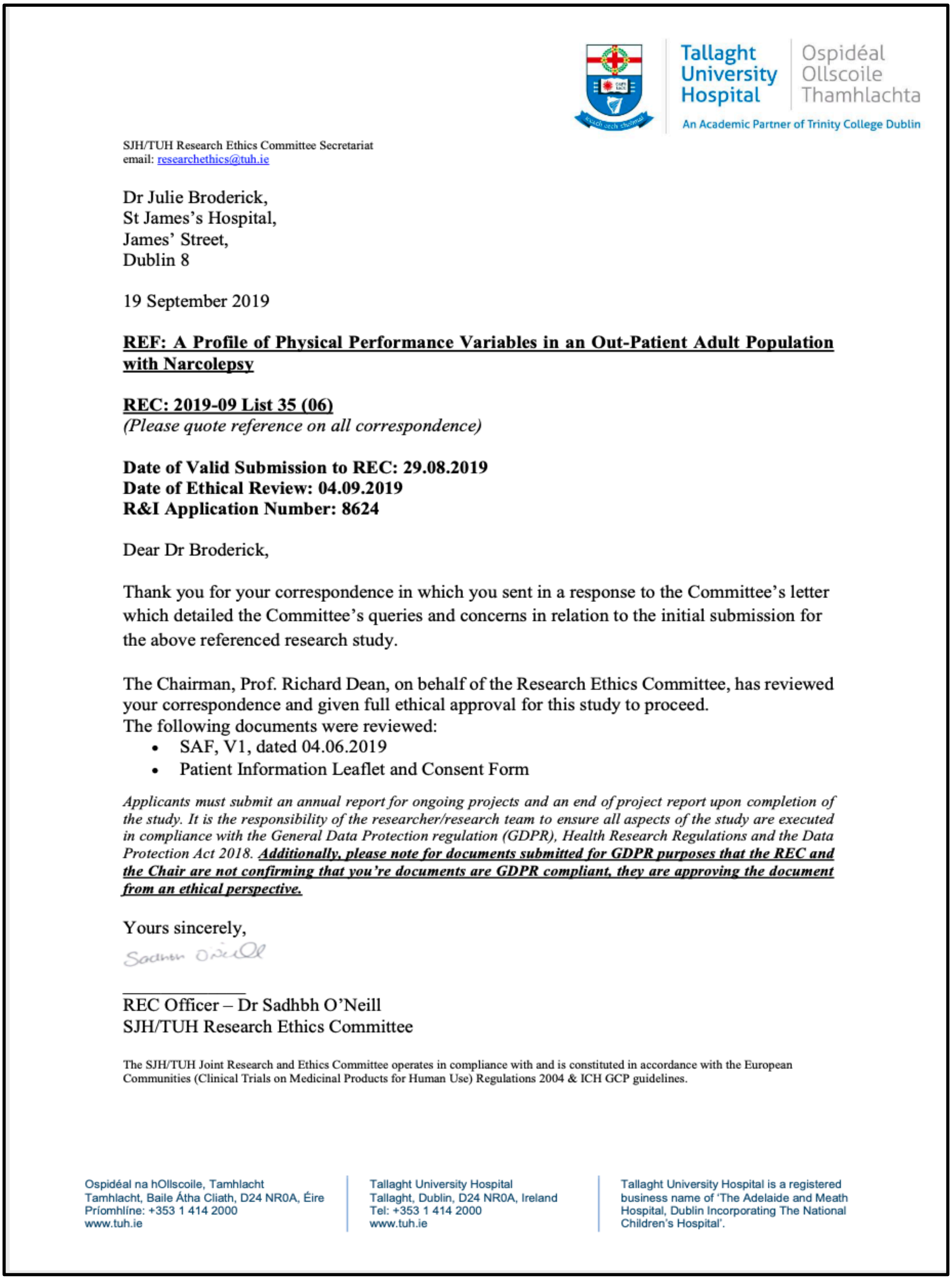
3. **Was the exposure measured in a valid and reliable way?**

   The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.
   Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. **Were objective, standard criteria used for measurement of the condition?**

   It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics.

Appendix V: Letter of Ethical Approval



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

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

Dr Julie Broderick,
St James's Hospital,
James' Street,
Dublin 8

19 September 2019

REF: A Profile of Physical Performance Variables in an Out-Patient Adult Population with Narcolepsy

REC: 2019-09 List 35 (06)
(Please quote reference on all correspondence)

Date of Valid Submission to REC: 29.08.2019
Date of Ethical Review: 04.09.2019
R&I Application Number: 8624

Dear Dr Broderick,

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 initial submission for the above referenced research study.

The Chairman, Prof. Richard Dean, on behalf of the Research Ethics Committee, has reviewed your correspondence and given full ethical approval for this study to proceed.
The following documents were reviewed:

- SAF, V1, dated 04.06.2019
- Patient Information Leaflet and Consent Form

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.

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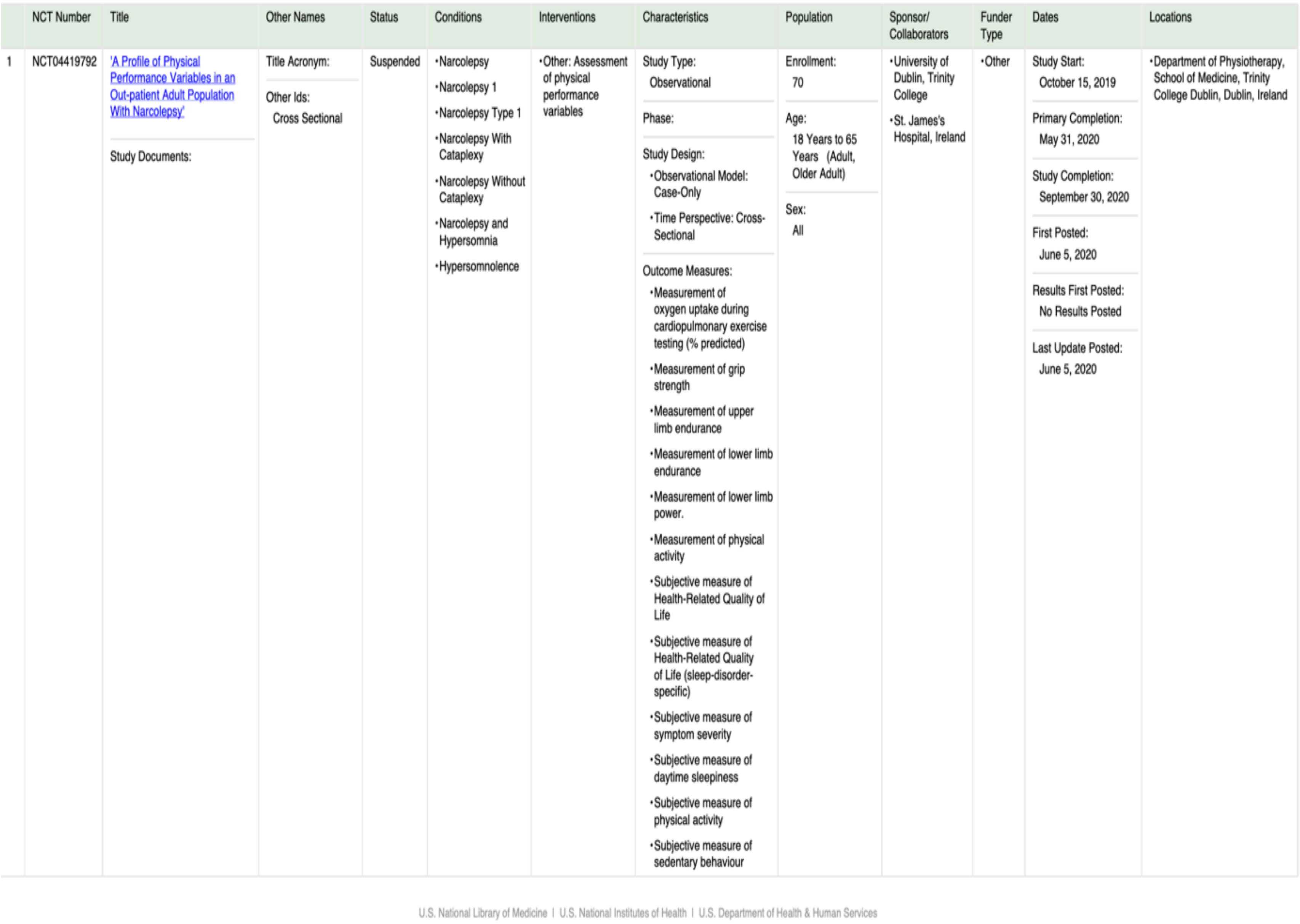
Tel: +353 1 414 2000
www.tuh.ie

Tallaght University Hospital is a registered business name of 'The Adelaide and Meath Hospital, Dublin Incorporating The National Children's Hospital'.

Appendix VI: Study Registration at ClinicalTrials.gov



	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
1	NCT04419792	'A Profile of Physical Performance Variables in an Out-patient Adult Population With Narcolepsy' Study Documents:	Title Acronym: Other Ids: Cross Sectional	Suspended	•Narcolepsy •Narcolepsy 1 •Narcolepsy Type 1 •Narcolepsy With Cataplexy •Narcolepsy Without Cataplexy •Narcolepsy and Hypersomnia •Hypersomnolence	•Other: Assessment of physical performance variables	Study Type: Observational Phase: Study Design: •Observational Model: Case-Only •Time Perspective: Cross-Sectional Outcome Measures: •Measurement of oxygen uptake during cardiopulmonary exercise testing (% predicted) •Measurement of grip strength •Measurement of upper limb endurance •Measurement of lower limb endurance •Measurement of lower limb power. •Measurement of physical activity •Subjective measure of Health-Related Quality of Life •Subjective measure of Health-Related Quality of Life (sleep-disorder-specific) •Subjective measure of symptom severity •Subjective measure of daytime sleepiness •Subjective measure of physical activity •Subjective measure of sedentary behaviour	Enrollment: 70 Age: 18 Years to 65 Years (Adult, Older Adult) Sex: All	•University of Dublin, Trinity College •St. James's Hospital, Ireland	•Other	Study Start: October 15, 2019 Primary Completion: May 31, 2020 Study Completion: September 30, 2020 First Posted: June 5, 2020 Results First Posted: No Results Posted Last Update Posted: June 5, 2020	•Department of Physiotherapy, School of Medicine, Trinity College Dublin, Dublin, Ireland

U.S. National Library of Medicine I U.S. National Institutes of Health I U.S. Department of Health & Human Services

Appendix VII: Study Protocol Publication

HRB Open Research

HRB Open Research 2020, 3:42 Last updated: 03 JUL 2020

Check for updates

STUDY PROTOCOL

Study protocol: A profile of physical performance variables in an outpatient adult population with narcolepsy [version 1; peer review: awaiting peer review]

Ragy Tadrous [1], Deirdre O'Rourke[2], Niamh Murphy[3], Lisa Slattery[2], Gillian Quinn [3], Julie Broderick[1]

[1]Discipline of Physiotherapy, School of Medicine, Trinity College Dublin, Dublin, Dublin, D08 W9RT, Ireland
[2]Department of Neurology, St. James's Hospital, Dublin, Dublin, Dublin, D08 W9RT, Ireland
[3]Department of Physiotherapy, St. James's Hospital, Dublin, Dublin, Dublin, D08 W9RT, Ireland

v1 **First published:** 03 Jul 2020, **3**:42
https://doi.org/10.12688/hrbopenres.13086.1
Latest published: 03 Jul 2020, **3**:42
https://doi.org/10.12688/hrbopenres.13086.1

Open Peer Review

Reviewer Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

Abstract

Background: Narcolepsy is a sleep disorder characterised by excessive daytime sleepiness and significantly impacts quality of life. People with narcolepsy demonstrate many potential barriers to being physically fit and active, such as sleepiness and social isolation. Very little is known about how physical performance variables may be affected in people with narcolepsy. This study aims to profile the physical fitness of adults with narcolepsy and to explore the relationship between physical fitness and quality of life, symptom severity and disease duration in this cohort.

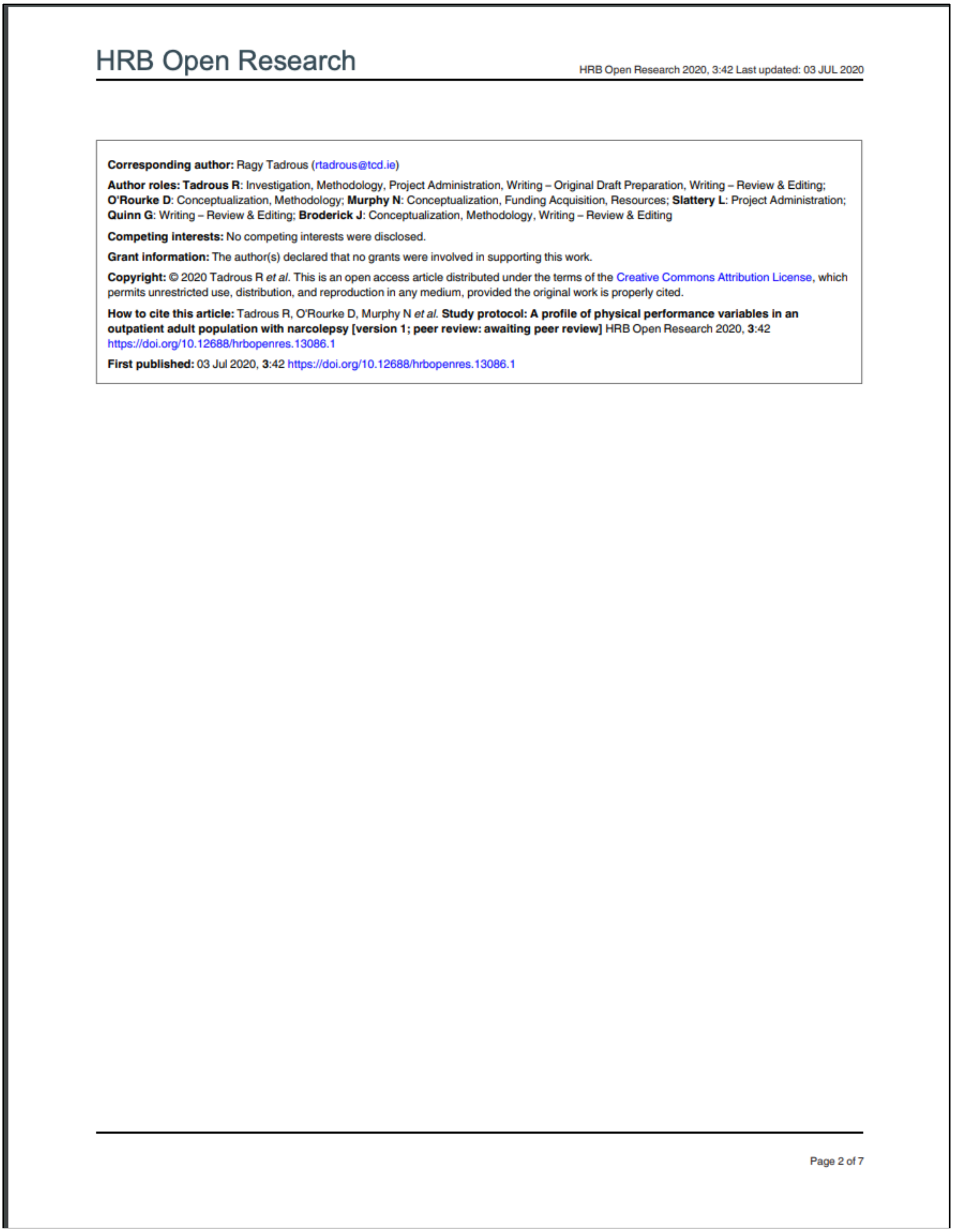
Methods and Analysis: In this cross-sectional observational study, participants will undergo a comprehensive physical performance test battery that will investigate cardiopulmonary fitness, objective measures of physical activity, muscle strength and endurance. Furthermore, quality of life, symptom severity and physical activity will be ascertained through self-report questionnaires. The study population will consist of adults with narcolepsy aged 18-65 years attending the National Narcolepsy Centre located in St. James's Hospital as an outpatient.

Ethics and Dissemination: Ethical approval has been obtained from the St. James's Hospital and Tallaght University Hospital Research Ethics Committee, and this study is presently underway. The results obtained from this study will be used to help tailor exercise and possible rehabilitation strategies for this population. Dissemination will be sought through peer-reviewed journals, national and international conferences, and through engagement with service user groups.

Registration: ClinicalTrials.gov Identifier NCT04419792; registered on 5 June 2020.

Keywords

Exercise, Physical Activity, Narcolepsy, Sleep Disorders, Quality of Life.



Corresponding author: Ragy Tadrous (rtadrous@tcd.ie)

Author roles: Tadrous R: Investigation, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **O'Rourke D**: Conceptualization, Methodology; **Murphy N**: Conceptualization, Funding Acquisition, Resources; **Slattery L**: Project Administration; **Quinn G**: Writing – Review & Editing; **Broderick J**: Conceptualization, Methodology, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Tadrous R, O'Rourke D, Murphy N *et al.* **Study protocol: A profile of physical performance variables in an outpatient adult population with narcolepsy [version 1; peer review: awaiting peer review]** HRB Open Research 2020, **3**:42 https://doi.org/10.12688/hrbopenres.13086.1

First published: 03 Jul 2020, **3**:42 https://doi.org/10.12688/hrbopenres.13086.1

Introduction

Narcolepsy is a sleep disorder that is characterised by excessive daytime sleepiness and is regularly associated with episodic muscular weakness, known as cataplexy, following intense emotions such as laughter or anger. Disrupted night-time sleep (DNS) is a common complaint in people with narcolepsy and can be accompanied by hallucinations and sleep paralysis (Roth *et al.*, 2013). With an estimated incidence of 25–50 per 100,000 in western populations (Overeem *et al.*, 2008), approximately 1200–2415 people live with narcolepsy in Ireland. Furthermore, Ireland, similar to other European countries (Heier *et al.*, 2013; Nohynek *et al.*, 2012; Partinen *et al.*, 2012; Szakacs *et al.*, 2013), has experienced an increased number of cases of narcolepsy following the 2009–2010 Swine Flu epidemic, with crude associations identified in pandemic-vaccination recipients (O'Flanagan *et al.*, 2014).

People with narcolepsy have a strong likelihood of experiencing occupational and social difficulties (Morse & Sanjeev, 2018) with strong links identified between narcolepsy, health care usage and unemployment (Jennum *et al.*, 2009). Narcolepsy can be disabling from a young age as over half will develop symptoms before 16 years of age (Thorpy & Krieger, 2014). Symptom onset is commonly associated with an increase in body mass, often resulting in obesity (Ponziani *et al.*, 2016). Additionally, higher incidences of chronic conditions including diabetes mellitus, sleep apnoea, chronic obstructive pulmonary disease, back pain, and arthritis have been observed in people with narcolepsy when compared to the general population (Jennum *et al.*, 2013). Furthermore, quality of life in people with narcolepsy is significantly lower than the general population, with physical role limitations and vitality commonly being the most affected quality of life domains (Becker *et al.*, 2004; Campbell *et al.*, 2011; Dodel *et al.*, 2007; Vignatelli *et al.*, 2004).

Correlations between physical fitness and symptom severity in narcolepsy are not fully understood and likely complex. A study conducted by Matoulek *et al.* (2017) identified that cardiorespiratory endurance was inversely correlated with sleepiness severity and the monthly frequency of cataplexy attacks in people with narcolepsy. However, people with narcolepsy typically have decreased opportunities to exercise and engage in leisurely pastimes due to sleepiness and social isolation, and less spontaneous activity has been noted in this population (Bruck *et al.*, 2005). A vicious cycle can develop with sedentary behaviour increasing sleepiness severity (Golden & Lipford, 2018), and the worsening of narcolepsy-related symptoms reducing activity levels and quality of life (Matoulek *et al.*, 2017). Additionally, this functional decline can lead to the secondary development of mental health problems, which can exacerbate the reduction in function and quality of life (Morse & Sanjeev, 2018).

This study aims to profile the physical performance of people with narcolepsy attending an outpatient clinic at St. James's Hospital, to ascertain the perception of unmet physical health needs, exercise habits and preferences. Secondary objectives of this study will be to explore the relationship between physical performance indices and sleep quality, functional ability, depression and quality of life in this population.

Methods

Study design

This study will be a cross-sectional study which will comprehensively profile the physical performance of adults attending a dedicated narcolepsy outpatient clinic at St. James's Hospital, Dublin.

Study population

Participants will be required to meet the following eligibility criteria: aged 18 to 65 years, diagnosis of type 1 or type 2 narcolepsy based on the International Classification of Sleep Disorders third edition criteria (American Academy of Sleep, 2014) for at least six months, eligibility screened by their treating clinician, and able to understand English and follow simple instruction to enable completion of assessments. Additionally, participants will be required to provide signed and informed consent to participate in the study, and for processing of their data to be eligible for participation. Individuals with sleep disorders other than narcolepsy, contraindications to moderate-intensity exercise, confirmed pregnancy or significant psychiatric illness or cognitive impairment will be excluded from participating in the study.

Recruitment

Potential participants will be screened by their treating clinicians in advance of their scheduled clinic visit, and sent an information leaflet at least 5–7 days before their appointment if deemed eligible to participate. A follow-up call from the specialist nurse will be made to answer any study-related questions. During their clinic visit, the primary study assessor (a research physiotherapist, R.T.) will approach potential participants and provide additional information regarding the study.

Assessment

The assessment will be divided into three components, described below.

I. Physical variables

Participants will be asked to undergo an expanded physiotherapy assessment which consists of measures of cardiovascular fitness and physical activity. The primary study assessor will conduct the following test battery:

Cardiopulmonary fitness will be assessed by the YMCA submaximal bike test to estimate VO$_2$ max (Golding *et al.*, 1989). The YMCA submaximal bike test is reported to have a moderately high correlation coefficient of $r = 0.79$, and when used to assess cardiopulmonary fitness in a heterogeneous population, Beekley *et al.* (2004) found no statistical difference between the predicted VO$_2$ max and the criterion measure (mean difference = 1.3 ml/kg^{-1}/min). The YMCA protocol uses two to four 3-minute stages of continuous exercise. The test is designed to raise the steady-state heart rate of the subject to between 110 beats per minute and 85% of the age-predicted maximal heart rate for at least two consecutive stages (American College of Sports Medicine, 2013).

Actigraphy. Physical activity and sedentary behaviour will be measured objectively through the use of actigraphy. Actigraphy is based on miniaturised acceleration sensors that translate physical motion to numeric representations (Sadeh *et al.*, 1995). Actigraphy utilises a portable device to collect movement information over prolonged periods of time (Berry, 2012). Actigraphy is based on the concept that movement is increased during waking hours and reduced during sleep (Littner *et al.*, 2003). The GTX3 model actigraph has strong relationships between counts per minute and VO_2 ($r=0.810$, $p<0.001$), and can reliably quantify physical activity when compared to oxygen consumption (Kelly *et al.*, 2013). Participants will be asked to wear the Actigraph around their waist for seven consecutive days, excluding swimming or bathing, and log the duration worn. Participants will be asked to post the Actigraph and wear time log to the study assessor in stamped addressed envelopes previously provided to them. Actigraph data will be downloaded and analysed using the ActiLife Software (ActiGraph Manufacturing Technology Inc., FL).

Lower body assessments. Vertical jump height and power will be measured through the countermovement jump test. The countermovement jump test correlates with sprint performance, maximal strength, and explosive-strength tests (Nuzzo *et al.*, 2008). When compared to other jump tests, the countermovement jump test is the most reliable measure of lower-body power (Markovic *et al.*, 2004). Furthermore, the countermovement jump test demonstrates great factorial validity through its relationship with explosive power (r = 0.87), low within-subject variation of 2.8% and high reliability with a Cronbach's alpha of 0.98 (Markovic *et al.*, 2004). Subjects are instructed to place chalk on their dominant hand. Participants will stand with their dominant shoulder about 6 inches (15 cm) from the wall and, with both feet flat on the floor, reach as high as possible with the dominant hand and make a chalk mark on the wall. They then lower their dominant hand and perform a countermovement by quickly flexing the knees and hips, moving the trunk forward and downward, and swinging their arms backwards. During the jump, the dominant arm reaches upward, and at the highest point in the jump, the participant places a second chalk mark on the wall with the fingers of the dominant hand using a swiping motion of the fingers. The score is the vertical distance between the two chalk marks. The best of three trials will be recorded to the nearest 0.5 inches or 1.0 cm (Haff & Triplett, 2015).

The isometric wall sit test is commonly used for evaluating endurance because it can be administered almost anywhere and is not complex (Tomchuk, 2011). Little equipment is necessary for the wall squat test, making it both cost-effective and accessible (Goldring *et al.*, 2014). The intra-class correlation coefficient for the wall squat test ranges from 0.69 to 0.88 (Lubans *et al.*, 2011). Participants will be instructed to place their back flat against the wall, with their toes pointed straight out and away from the wall. When instructed to go, the participant slides their back down the wall until their knees are at a 90-degree angle. This position is maintained until exhaustion, and only one trial is performed. The participants will be timed from the moment they obtain the proper test position until they can no longer maintain this position (Tomchuk, 2011).

Upper body assessment. Grip strength will be assessed using a handheld calibrated dynamometer (JAMAR, Hatfield, PA, USA). Although the relationship is not causative, grip strength has been reported to correlate with chronic health conditions (Bohannon, 2008; Massy-Westropp *et al.*, 2011). Low grip strength has been associated with low spinal and pelvic bone mineral density and increased risk of vertebral fractures in women (Dixon *et al.*, 2005). Additionally, longitudinal studies have identified strong inverse relationships between grip strength and all-cause mortality, mortality from cardiovascular disease, respiratory disease, and cancer (Celis-Morales *et al.*, 2018). The American Society of Hand Therapists recommends that the Jamar dynamometer is used as the gold standard for the assessment of grip strength (Fess *et al.*, 1992). The Jamar dynamometer has excellent test-retest reliability (ICC = 0.822), and interrater reliability (ICC = 0.996-0.998) as reported by Mathiowetz *et al.* (1984), and Lindstrom-Hazel *et al.* (2009), respectively. Furthermore, Jamar dynamometry has excellent concurrent validity between participant's dominant hand (ICC = 0.99) and non-dominant hand (ICC = 0.98) as reported by Bellace *et al.* (2000) Measurements will be obtained in standardised conditions and following testing conditions as outlined by the American Society of Hand Therapists (MacDermid *et al.*, 2015). The participants will be instructed to squeeze as hard as they can for 3 to 5 seconds. The procedure will be performed three times with each hand alternately, with an interval of one minute between each measurement (MacDermid *et al.*, 2015).

The American College of Sports Medicine (ACSM) Push-Up test will be used to assess the strength and endurance of the upper limb. The Push-up test is a simple, cost-effective measure that can provide an approximation of functional status (Yang *et al.*, 2019). Muscle strength and endurance have been shown to provide an independent protective effect for all-cause mortality and hypertension in healthy males (Artero *et al.*, 2011). Furthermore, longitudinal studies suggest that push up capacity is inversely related to the risk of cardiovascular disease, with individuals capable of performing 11 or more push-ups having significantly reduced risk of subsequent cardiovascular events (Yang *et al.*, 2019). The Push-Up test is highly reliable (r = 0.95 and 0.91) for predicting upper limb muscular endurance in collegiate students (Baumgartner *et al.*, 2002). The Push-Up test has a test-retest interclass correlation coefficient of 0.95, with a 95% confidence interval of 0.85-0.99 (Ryman Augustsson *et al.*, 2009). The maximal number of push-ups performed consecutively without rest is counted. The test is stopped when the participant strains forcibly or is unable to maintain the appropriate technique within two repetitions (ACSM, 2013).

Data management

In compliance with GDPR, data will only be shared with those in the project team. Data will be archived for seven years as per the institutional ethical obligations, in a password protected data drive for purposes including subsequent dissemination in peer-reviewed journals or at national and international conferences. A Data Protection Impact Assessment form has been completed and submitted to the Data Impact Officer in Trinity College Dublin. This ensures that the risks associated with processing personal data and the impact on individuals are minimised throughout the proposed research. In order to prevent unauthorised consultation, alteration, disclosure or erasure of the collected data, the following strategies will be employed:

I. Hard copies of the data collected during the study will be filed and stored in a locked cabinet within the Physiotherapy Department in St James's Hospital for the minimal time period possible in compliance with GDPR.

II. The electronic data will be stored on a networked computer, with hard disk encryption provided by St. James's Hospital.

III. Strong encryption software and passwords will be used to protect collected data, and will only be accessible to authorised data processors. The most secure versions of all software packages will be run and will be protected by anti-virus software.

IV. Every available step will be taken to ensure GDPR compliance by ensuring computing devices used for this study are safe and secure.

Discussion

Very little is known about physical performance variables of people with narcolepsy. This article presents a study protocol to comprehensively profile physical performance of people with narcolepsy and explore the relationship between physical variables, quality of life, symptom severity and disease duration. Conduction of a comprehensive physical performance test battery will facilitate the establishment of population-specific normative values and enable comparison to the general population. Furthermore, through establishing the normative values for the cardiovascular fitness, physical activity, strength and power of this population, considerable insight will be provided to help tailor exercise and possible physical rehabilitation strategies for this population. Strengths of this protocol include a broad and representative sample, as this study will be undertaken in the National Narcolepsy Centre for Ireland, located in St. James's Hospital and the robust physical performance measures employed in this study. Limitations of this proposed protocol include that this is a novel research area, and as such, it is difficult to do a formal sample size calculation.

Data availability

No data are associated with this article.

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Appendix VIII: Participant Information Leaflet and Consent Form

ST. JAMES'S HOSPITAL
James's Street, Dublin 8
Telephone (+353 1) 410 3000
www.stjames.ie

PARTICIPANT INFORMATION LEAFLET

Study Title:
'A profile of physical performance variables in an out-patient adult population with Narcolepsy'

Principal Investigator(s) and Co-investigator(s): Dr. Deirdre O' Rourke, Dr. Julie Broderick

You are being asked to participate in a research study which takes place in the Narcolepsy Out-patient clinic of St. James's Hospital which is led by Dr. Deirdre O' Rourke (Medical Consultant). Before you decide whether or not you wish to take part, 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. You may wish to discuss it with your family, friends or GP.

PART 1 – THE STUDY

Why is this study being done?

It is known that narcolepsy is a serious long term disorder that affects the control of sleep and wakefulness. Little is known about how narcolepsy affects physical variables such as fitness, strength and physical activity levels, or how physical fitness affects the symptoms of narcolepsy. Without knowing this information, it is difficult to advise on suitable exercise and how to plan suitable follow-on services if needed.

Why am I being asked to take part?

You have been chosen to participate as you have been diagnosed with Narcolepsy and you are attending the Narcolepsy out-patient services of St. James's Hospital.

Do I have to take part? What happens if I say no? Can I withdraw?

Your decision whether to participate or not is entirely voluntary. If you decide not to take part it will not affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it will not affect your current or future medical care. You do not have to give a reason for not taking part or for opting out. If you decide not to participate, this will have no adverse consequences and make no difference to your routine care and treatment. If you wish to opt out, please contact the physiotherapy study investigator Mr Ragy Tadrous, (rtadrous@tcd.ie) who will be able to organise this for you.

How will the study be carried out?

If you consent to participate, you will undergo a number of straight forward tests to assess your fitness, strength, physical activity and other physical variables, which will take place in the Outpatient Clinic of St. James's Hospital, at a convenient time around your routine clinical appointment, or at another time convenient for you. There are also questionnaires about sleep, quality of life and physical activity levels and a small number of questions relating to how you feel about your physical health. It is planned that about 70 patients will take part in the study.

What will happen to me if I agree to take part?

If you agree to take part, a physiotherapy researcher will carry out basic physical tests such as a treadmill or bike fitness test and tests of strength and power. These will take place as part of your routine visit to the out-patient clinic, or at another time convenient for you. You can stop, take a break, or opt out of the study at any time, without any change to your normal treatment in any way.

You will meet a physiotherapy researcher who will carry out the tests with you. No tests are invasive or uncomfortable in any way. The whole assessment will take about 20 minutes.

Are there any benefits to me or others if I take part in the study?

There may not be any major direct benefits to you from participating or taking part in this study. But, by participating in this study you will be taking part in a more detailed physical assessment. This may help highlight areas which need more focussed physical treatment. This may also make you more aware of your own physical status.

Are there any risks to me or others if I take part in the study?

There are minimal risks to participation in this study. There is a slight risk of injury during the physiotherapy assessment as we will be asking you to use a treadmill or bike and carry out other basic physical tests. However, you will not be asked to perform any tests which you are not able for and you will be fully supervised at all times so the risks involved are very small. You can also stop or take a break at any time should you wish.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

The study investigator can discuss with you the outcome of the physical tests performed as part of this study. It is planned that results of this study will be presented together in a non-identifiable way in suitable medical conferences and journals.

[redacted]

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

To help decide if you would be suitable to participate in this study, your medical records will be accessed by your treating clinician. If you consent to participate the following information will be taken from your medical chart; your age, gender, previous medical history and medication. Your data will be given a code and will not be identifiable.

What will happen my personal data?

Arrangements have been put in place so that personal data will be processed only as is necessary to achieve the objective of this research and will not be processed in a way that could cause any possible damage or distress. To comply with local regulations, your data will be kept in a coded form for 5 years and then destroyed. Your data will strictly only be used for this purposes of this project based in St. James's Hospital.

Who will access and use my personal data as part of this study?

Only those working directly on this project (Dr. Deirdre O' Rourke and the physiotherapy study investigator) will have access to your personal data and this will be solely for the purposes of this study. Personal data will not be sought from other healthcare providers or disclosed to anyone else.

Will my personal data be kept confidential? How will my data be kept safe?

Your data will be stored securely in encrypted files - so only the study investigators can access them. An assessment of the data protection implications of this health research and/or a data protection impact assessment has been carried out which has revealed a low level of risk. No future presentation or publication of this research could identify any study participant as data will be coded and analysed together.

What is the lawful basis to use my personal data?

The **lawful basis** for the use of your personal data is Article 6 and Article 9 of GDPR.

Who can I contact if I have any queries in relation to my personal data?

If you have any concerns in relation to the use of your data you can contact the data protection officer in St. James's Hospital, Mr. Cathal Kinsella (dataprotection@stjames.ie).

What are my rights?

You have a right to withdraw your consent to participation in this study

You have the right to withdraw consent to your personal data being used in this research project. You will be able to do this by contacting the Principal Investigator Dr Deirdre O' Rourke, Medical Consultant, PO Box 580, James's Street, Dublin 8, Tel 01 410 3000

You have a right to request access to data held about yourself by the study investigators

You have a right to restrict or object to processing of your data

You have a right to have any inaccurate information about yourself corrected or deleted.

You have a right to data portability, meaning you have a right to move your data from one controller to another in a readable format.

You have a right to object to automated processing including profiling.

You have a right to lodge a complaint with the Data Protection Commissioner (data protection@stjames.ie).

[redacted]

Will it cost me anything if I agree to take part?

There will be no costs to you for taking part in this study. The assessment conducted for this study will take place as part of your routine clinic visit to the Out-patient Clinic of St. James's Hospital. Your doctors are insured by the State Claims Insurance Service.

Who is funding this study? Will the results study be used for commercial purposes?

There is no funding for this study. The results will not be used for commercial purposes.

Has this study been approved by a research ethics committee?

This study has been approved by the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee.

[redacted]

Will my personal data be used in future studies?

Your consent is sought for the processing or use of necessary data for the present study only. This will not be used for any future research studies.

[redacted]

Where can I get further information?

- Principal Investigator: Dr. Deirdre O' Rourke (Consultant Medical Physician)
- Data Controllers: St. James's Hospital, Trinity College Dublin
- Data Processor(s): Physiotherapy Study Investigator Ragy Tadrous

What happens if I wish to make a complaint?

If you wish to make a complaint, there are a number of ways that you can give us your feedback. You can contact the Patient Experience Office by post, by email, by telephone, or by appointment. The telephone number is 01 4284248 or 01 4103361.

The email address patientfeedback@stjames.ie. The postal address is Patient Experience Office, Quality and Safety Office, St James's Hospital, Dublin 8.

Will I be contacted again?

This study is carried out as part of your routine clinical visit and does not necessitate another appointment.

ST. JAMES'S HOSPITAL
James's Street, Dublin 8
Telephone (+353 1) 410 3000
www.stjames.ie

CONSENT FORM

Study Title: 'A profile of physical performance variables in an out-patient adult population with Narcolepsy'

To be completed by the **PARTICIPANT**:

I have read and understood the information leaflet.	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.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.	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 ☐
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 (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:	

Appendix IX: Short Form 36 (SF36)

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)

Excellent ☐
Very Good ☐
Good ☐
Fair ☐
Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)

Much better than one year ago ☐
Somewhat better now than one year ago ☐
About the same as one year ago ☐
Somewhat worse now than one year ago ☐
Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**Not Limited At All**
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
(Please circle one number on each line.)

		Yes	**No**
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?
(Please circle one number on each line.)

		Yes	**No**
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

Not at all ☐
Slightly ☐
Moderately ☐
Quite a bit ☐
Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

None ☐
Very mild ☐
Mild ☐
Moderate ☐
Severe ☐
Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

Not at all ☐
A little bit ☐
Moderately ☐
Quite a bit ☐
Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

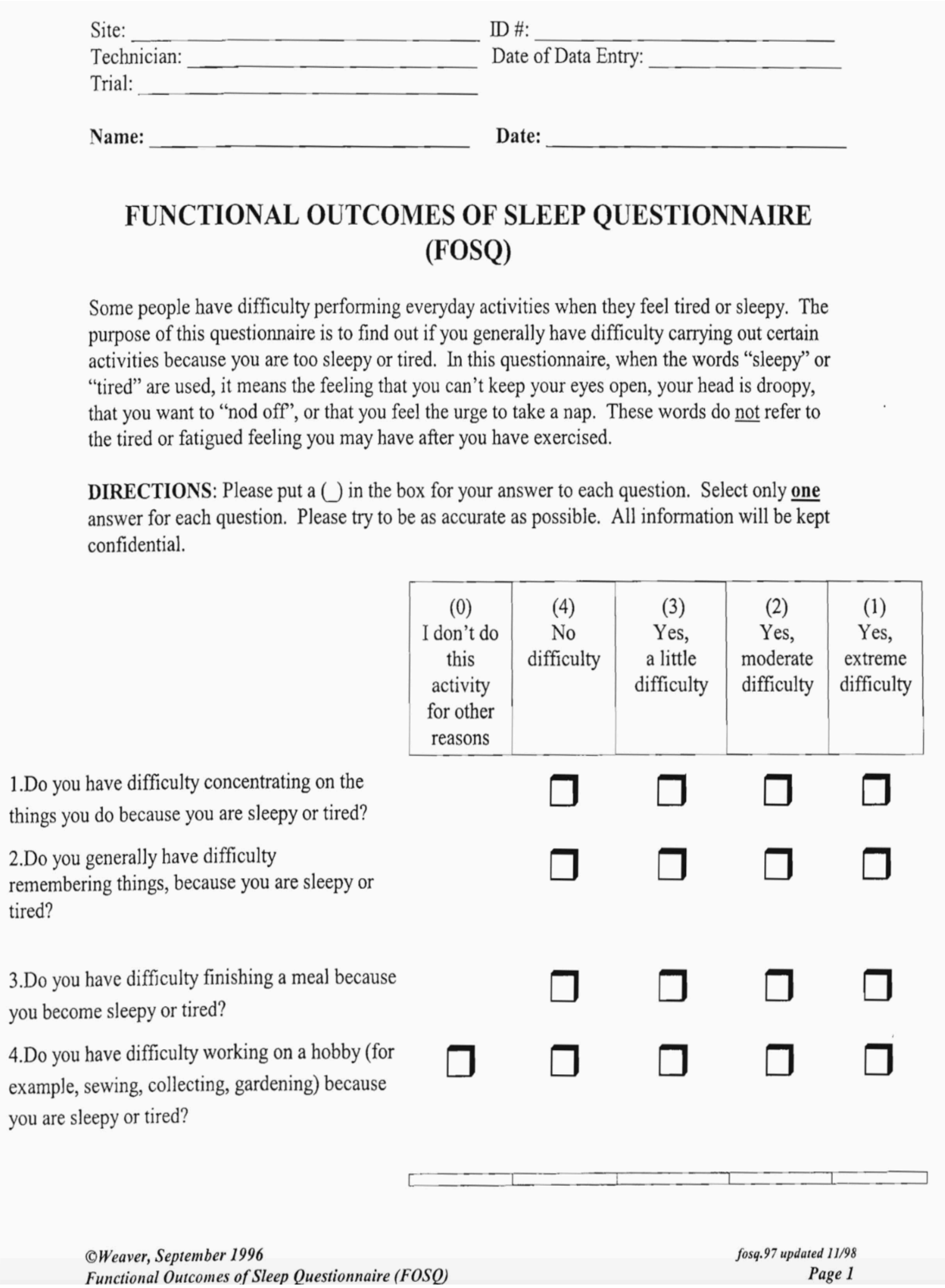
All of the time ☐
Most of the time ☐
Some of the time ☐
A little of the time ☐
None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

Appendix X: Functional Outcomes of Sleep Questionnaire (FOSQ)



Site: ____________________ ID #: ____________________
Technician: ____________________ Date of Data Entry: ____________________
Trial: ____________________

Name: ____________________ **Date:** ____________________

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. These words do <u>not</u> refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please put a (_) in the box for your answer to each question. Select only **<u>one</u>** answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1.Do you have difficulty concentrating on the things you do because you are sleepy or tired?		☐	☐	☐	☐
2.Do you generally have difficulty remembering things, because you are sleepy or tired?		☐	☐	☐	☐
3.Do you have difficulty finishing a meal because you become sleepy or tired?		☐	☐	☐	☐
4.Do you have difficulty working on a hobby (for example, sewing, collecting, gardening) because you are sleepy or tired?	☐	☐	☐	☐	☐

Functional Outcomes of Sleep Questionnaire (FOSQ)

fosq.97 updated 11/98
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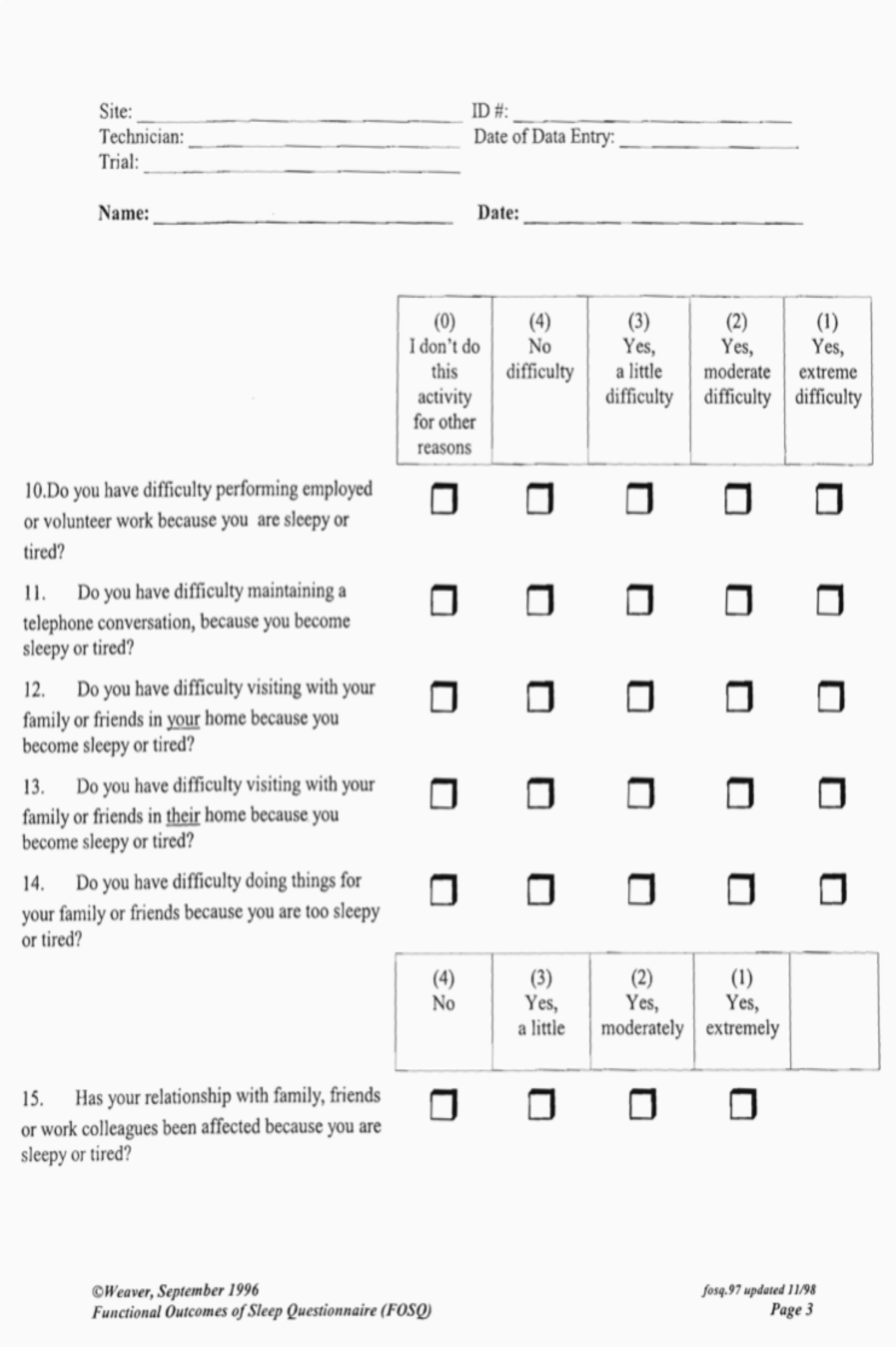
Site: ______________________ ID #: ______________________
Technician: ______________________ Date of Data Entry: ______________________
Trial: ______________________

Name: ______________________ **Date:** ______________________

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5.Do you have difficulty doing work around the house (for example, cleaning house, doing laundry, taking out the trash, repair work) because you are sleepy or tired?	☐	☐	☐	☐	☐
6.Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?	☐	☐	☐	☐	☐
7.Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?	☐	☐	☐	☐	☐
8.Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?	☐	☐	☐	☐	☐
9.Do you have difficulty taking care of financial affairs and doing paperwork (for example, writing checks, paying bills, keeping financial records, filling out tax forms, etc.) because you are sleepy or tired?	☐	☐	☐	☐	☐



Site: ____________________ ID #: ____________________
Technician: ____________________ Date of Data Entry: ____________________
Trial: ____________________

Name: ____________________ **Date:** ____________________

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
10.Do you have difficulty performing employed or volunteer work because you are sleepy or tired?	☐	☐	☐	☐	☐
11. Do you have difficulty maintaining a telephone conversation, because you become sleepy or tired?	☐	☐	☐	☐	☐
12. Do you have difficulty visiting with your family or friends in <u>your</u> home because you become sleepy or tired?	☐	☐	☐	☐	☐
13. Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	☐	☐	☐	☐	☐
14. Do you have difficulty doing things for your family or friends because you are too sleepy or tired?	☐	☐	☐	☐	☐

	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely	
15. Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	☐	☐	☐	☐	

Functional Outcomes of Sleep Questionnaire (FOSQ)

Site: ______________________________ ID #: __________________________
Technician: _________________________ Date of Data Entry: _______________
Trial: ______________________________

Name: ____________________________ **Date:** __________________________

In what way has your relationship been affected? ____

____

____

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
16. Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	☐	☐	☐	☐	☐
17. Do you have difficulty watching a movie or videotape because you become sleepy or tired?	☐	☐	☐	☐	☐
18. Do you have difficulty enjoying the theater or a lecture because you become sleepy or tired?	☐	☐	☐	☐	☐
19. Do you have difficulty enjoying a concert because you become sleepy or tired?	☐	☐	☐	☐	☐
20. Do you have difficulty watching TV because you are sleepy or tired?	☐	☐	☐	☐	☐
21. Do you have difficulty participating in religious services, meetings or a group or club, because you are sleepy or tired?	☐	☐	☐	☐	☐

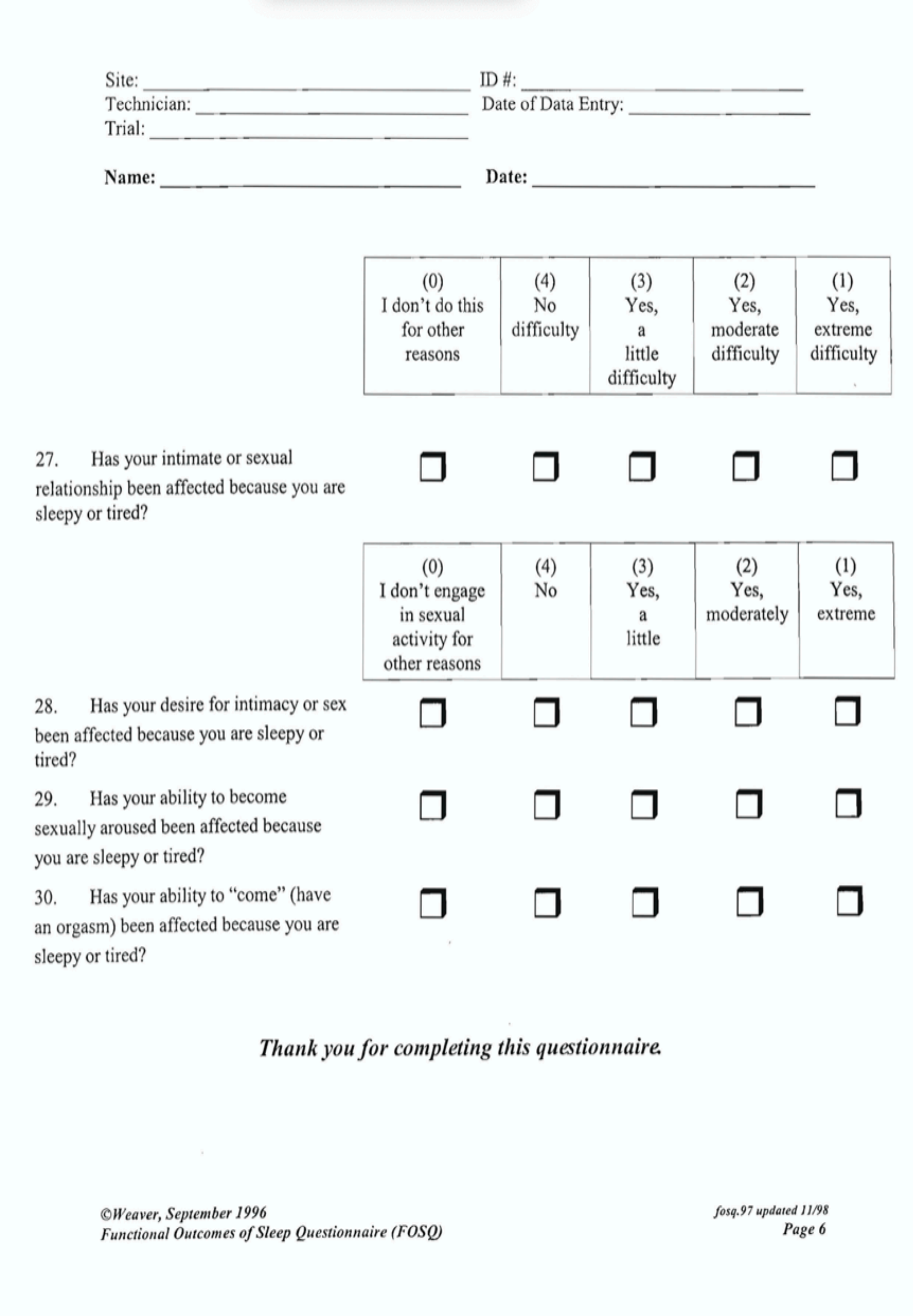
Site: ______________________ ID #: ______________________
Technician: ______________________ Date of Data Entry: ______________
Trial: ______________________

Name: ______________________ **Date:** ______________________

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
22. Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?		☐	☐	☐	☐
23. Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?		☐	☐	☐	☐

	(0) I don't do this for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
24. Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?		☐	☐	☐	☐
25. Do you have difficulty keeping pace with others your own age because you are sleepy or tired?		☐	☐	☐	☐

	(1) Very Low	(2) Low	(3) Medium	(4) High
26. How would you rate your general level of activity?	☐	☐	☐	☐



Site: ____________________ ID #: ____________________
Technician: ____________________ Date of Data Entry: ____________________
Trial: ____________________

Name: ____________________ **Date:** ____________________

	(0) I don't do this for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
27. Has your intimate or sexual relationship been affected because you are sleepy or tired?	☐	☐	☐	☐	☐

	(0) I don't engage in sexual activity for other reasons	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extreme
28. Has your desire for intimacy or sex been affected because you are sleepy or tired?	☐	☐	☐	☐	☐
29. Has your ability to become sexually aroused been affected because you are sleepy or tired?	☐	☐	☐	☐	☐
30. Has your ability to "come" (have an orgasm) been affected because you are sleepy or tired?	☐	☐	☐	☐	☐

Thank you for completing this questionnaire.

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Functional Outcomes of Sleep Questionnaire (FOSQ)

fosq.97 updated 11/98
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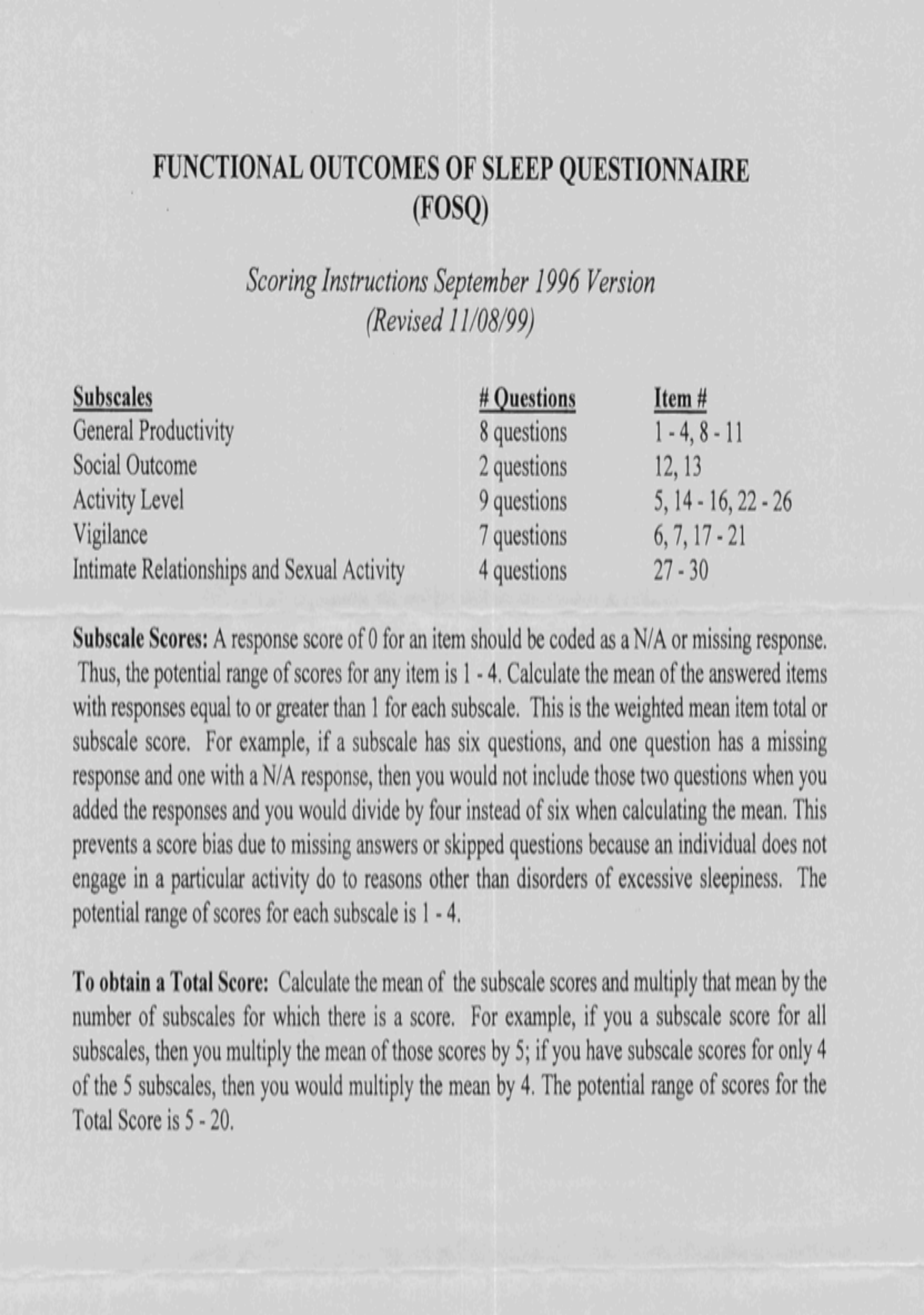


FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE
(FOSQ)

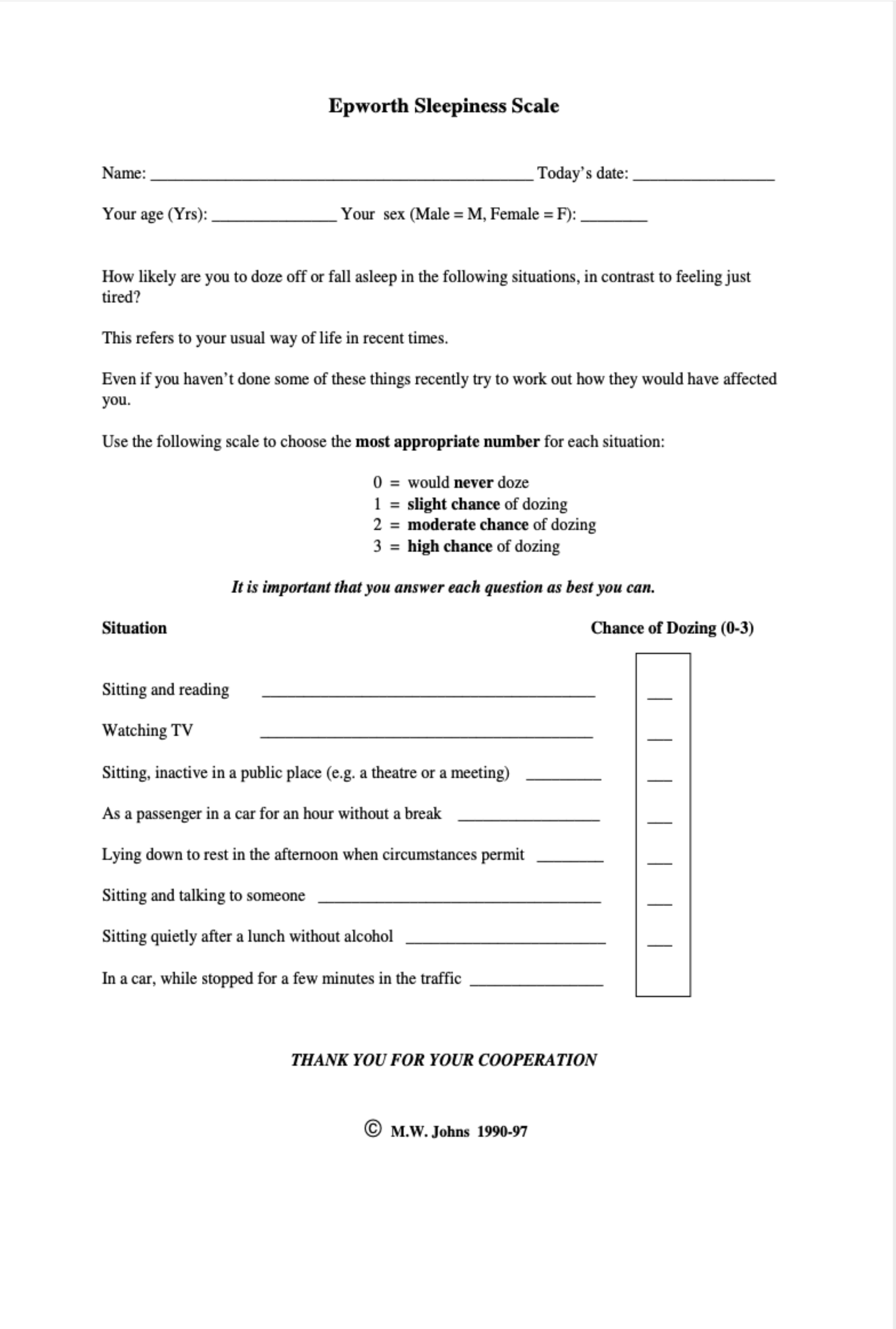
Scoring Instructions September 1996 Version
(Revised 11/08/99)

Subscales	**# Questions**	**Item #**
General Productivity	8 questions	1 - 4, 8 - 11
Social Outcome	2 questions	12, 13
Activity Level	9 questions	5, 14 - 16, 22 - 26
Vigilance	7 questions	6, 7, 17 - 21
Intimate Relationships and Sexual Activity	4 questions	27 - 30

Subscale Scores: A response score of 0 for an item should be coded as a N/A or missing response. Thus, the potential range of scores for any item is 1 - 4. Calculate the mean of the answered items with responses equal to or greater than 1 for each subscale. This is the weighted mean item total or subscale score. For example, if a subscale has six questions, and one question has a missing response and one with a N/A response, then you would not include those two questions when you added the responses and you would divide by four instead of six when calculating the mean. This prevents a score bias due to missing answers or skipped questions because an individual does not engage in a particular activity do to reasons other than disorders of excessive sleepiness. The potential range of scores for each subscale is 1 - 4.

To obtain a Total Score: Calculate the mean of the subscale scores and multiply that mean by the number of subscales for which there is a score. For example, if you a subscale score for all subscales, then you multiply the mean of those scores by 5; if you have subscale scores for only 4 of the 5 subscales, then you would multiply the mean by 4. The potential range of scores for the Total Score is 5 - 20.

Appendix XI: Epworth Sleepiness Scale (ESS)



Epworth Sleepiness Scale

Name: ______________________________ Today's date: ______________

Your age (Yrs): ____________ Your sex (Male = M, Female = F): ________

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading ______________________	___
Watching TV ______________________	___
Sitting, inactive in a public place (e.g. a theatre or a meeting) _________	___
As a passenger in a car for an hour without a break ____________	___
Lying down to rest in the afternoon when circumstances permit ________	___
Sitting and talking to someone ____________________	___
Sitting quietly after a lunch without alcohol ______________	___
In a car, while stopped for a few minutes in the traffic ____________	

THANK YOU FOR YOUR COOPERATION

Appendix XII: Narcolepsy Severity Scale (NSS)

Narcolepsy Severity Scale (NSS)

For your answer, please consider mainly the signs of your illness *during the last month*.

Item NSS01: Did you experience an irresistible need to sleep during the day? If yes, how many episodes?
005: >1 episode per day
004: >1 episode per week
003: > 1 episode per month
002: >1 episode per year
001: <1 episode a year
000: Never

Item NSS02: Are you worried about falling asleep (without noticing it, suddenly,…) during the day?
003: Very worried
002: Worried
001: Not very worried
000: Not worried at all

Item NSS03: How important is the disruption of your work/activities caused by these daytime sleep attacks?
003: Very important
002: Important
001: Moderately Important
000: Not important at all/I did not have daytime sleep attacks

Item NSS04: How important is the disruption of your social and family life by these daytime sleep attacks?
003: Very important
002: Important
001: Moderately important
000: Not important at all/I did not have daytime sleep attacks

Item NSS05: How do you feel generally after one of such daytime sleep attacks?
000: Very refreshed/no new sleep attack
001: Refreshed
002: Tired
003: Very tired

Item NSS06: After a daytime sleep attack, how much time will pass before the next daytime sleep attack?
005: < 1 hour
004: Between 1 and 3 hours
003: Between 3 and 6 hours
002: Between 6 and 8 hours
001: > 8 hours
000: I do not usually have another daytime sleep attack before bedtime

Item NSS07: To what extent do these sudden daytime sleep attacks affect your ability to drive a car?
003: Very much
002: Much
001: Not too much
000: Not at all/I do not drive for other reasons

Item NSS08: How frequently do you have episodes of generalized cataplexy when experiencing emotions (laughter, intense pleasure, surprise) (generalized cataplexy = loss of muscle tone all over, collapse or cannot move)
005: >1 episode a day
004: >1 episode a week
003: >1 episode a month
002: >1 episode a year
001: <1 episode a year
000: Never, no generalized cataplexy

Item NSS09: How frequently do you have episodes of partial cataplexy (only face, neck, arms, or knees) when experiencing emotions?
005: >1 episode a day
004: >1 episode a week
003: >1 episode a month
002: >1 episode a year
001: <1 episode a year
000: Never, no partial cataplexy

Item NSS10: How much is your work, social or family life affected by these episodes of cataplexy?
003: Very much
002: Much
001: Not very much
000: Not at all/no cataplexy

Item NSS11: How frequently do you have hallucinations when falling asleep or waking up?
005: >1 episode a day
004: >1 episode a week
003: >1 episode a month
002: >1 episode a year
001: <1 episode a year
000: Never, no hallucinations

Item NSS12: To what extent are you bothered by these hallucinations?
003: Very bothered
002: Bothered
001: Not very bothered
000: Not bothered at all/no hallucination

Item NSS13: How frequently do you experience sleep paralysis when falling asleep or waking up
005: >1 episode a day
004: >1 episode a week
003: >1 episode a month
002: >1 episode a year
001: <1 episode a year
000: Never, no sleep paralysis

Item NSS14: To what extent are you bothered by these sleep paralysis episodes?
003: Very bothered
002: Bothered
001: Not very bothered
000: Not bothered at all/no sleep paralysis

Item NSS15: Currently, how disturbed is your nighttime sleep?
003: Very much
002: Much
001: Not too much
000: Not at all

Appendix XIII: Physical Activity Vital Sign (PAVS)

Physical Activity Vital Sign

Exercise is Medicine®
AMERICAN COLLEGE of SPORTS MEDICINE®

1. On average, how many days per week do you engage in moderate to strenuous exercise (like a brisk walk)? _____ days
2. On average, how many minutes do you engage in exercise at this level? _____ minutes

Total minutes per week of physical activity (multiply #1 by #2) _____ **minutes per week**

Incorporate the PAVS into your electronic health record and patient intake forms. Calculations may be programmed and the sedentary patient flagged for referral or counseling.

Using the Physical Activity Vital Sign

National guidelines recommend 150 minutes per week of moderate intensity physical activity. That's just 2 ½ hours out of 168 hours in a week! In place of moderate intensity activity, you can also complete 75 minutes of vigorous intensity physical activity, or an equivalent combination of moderate and vigorous intensity physical activity.

What's Moderate Intensity?

- You can talk, but not sing, while performing the activity.
- Examples: brisk walking, slow biking, doubles tennis, various forms of dance, active home chores and gardening, etc.

What's Vigorous Intensity?

- Vigorous intensity: You can no longer talk easily during the activity and are somewhat out of breath.
- Examples: jogging, fast bicycling, singles tennis, aerobic exercise class, swimming laps, etc.

You can also achieve 150 minutes through a combination of moderate and vigorous intensity physical activity.

- 1 minute of vigorous activity is equal to 2 minutes of moderate activity.
- If activity is done throughout the day, you can perform multiple "bouts" of any length to add up to the recommended 150 minutes/week.

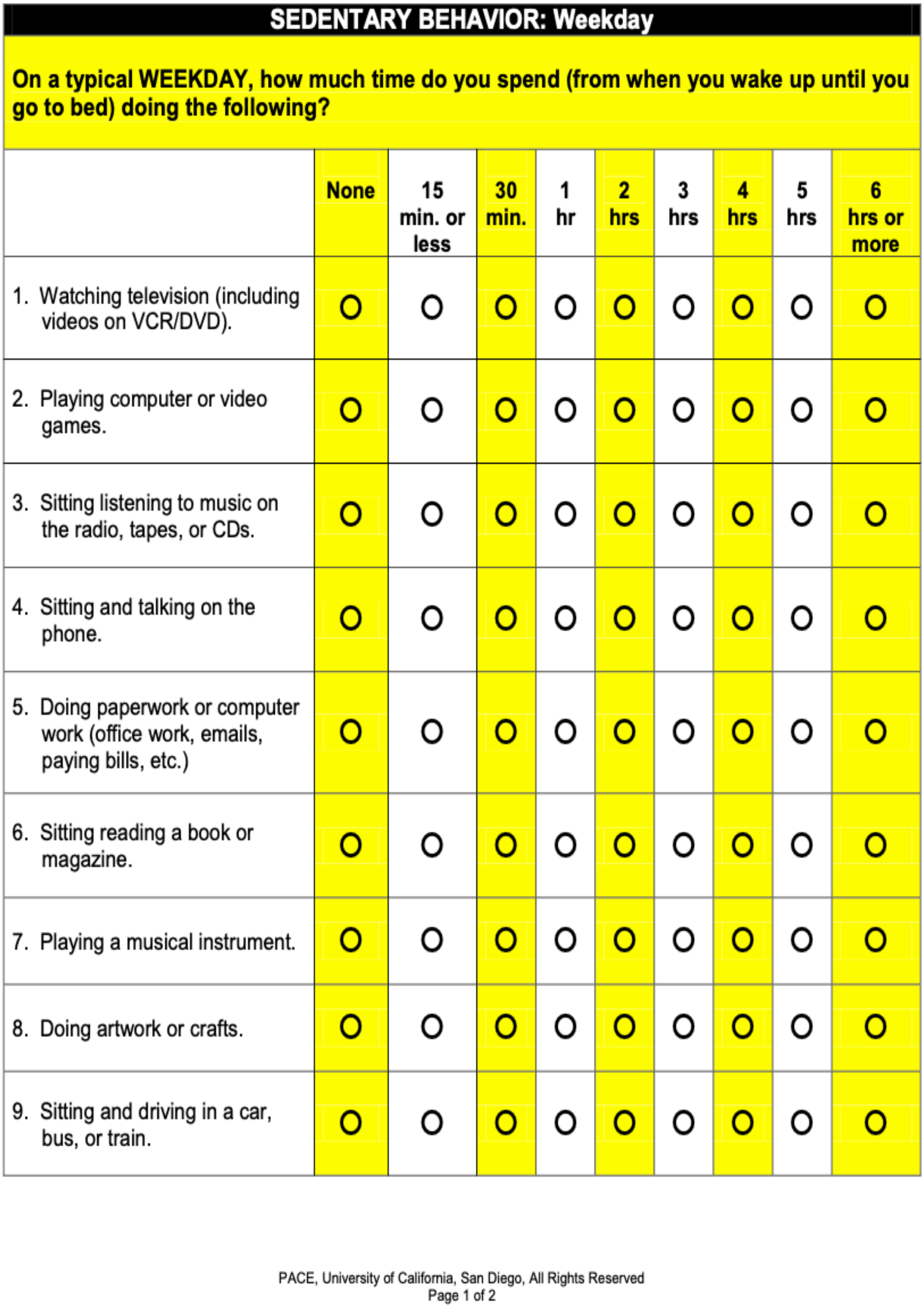
If your patient is NOT achieving 150 minutes a week of physical activity, help the patient to set more realistic goals to gradually increase either their frequency or duration until they are capable of safely achieving the national recommendations.

The Physical Activity Vital Sign – Other Considerations

- A comprehensive assessment of physical activity should include promotion of active living throughout the day to reduce sedentary time/screen time, as well as muscle strengthening exercises as recommended by the Physical Activity Guidelines for Americans: Adults should do muscle strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week.
- If you wish to add a question on muscle strengthening activities, we recommend the following:

How many days a week do you perform muscle strengthening exercises, such as bodyweight exercises or resistance training? _____ days

Appendix XIV: Sedentary Behaviour Questionnaire (SEDBQ)



SEDENTARY BEHAVIOR: Weekday

On a typical WEEKDAY, how much time do you spend (from when you wake up until you go to bed) doing the following?

	None	15 min. or less	30 min.	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs or more
1. Watching television (including videos on VCR/DVD).	○	○	○	○	○	○	○	○	○
2. Playing computer or video games.	○	○	○	○	○	○	○	○	○
3. Sitting listening to music on the radio, tapes, or CDs.	○	○	○	○	○	○	○	○	○
4. Sitting and talking on the phone.	○	○	○	○	○	○	○	○	○
5. Doing paperwork or computer work (office work, emails, paying bills, etc.)	○	○	○	○	○	○	○	○	○
6. Sitting reading a book or magazine.	○	○	○	○	○	○	○	○	○
7. Playing a musical instrument.	○	○	○	○	○	○	○	○	○
8. Doing artwork or crafts.	○	○	○	○	○	○	○	○	○
9. Sitting and driving in a car, bus, or train.	○	○	○	○	○	○	○	○	○

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Page 1 of 2

SEDENTARY BEHAVIOR: Weekday

On a typical WEEKDAY, how much time do you spend (from when you wake up until you go to bed) doing the following?

	None	15 min. or less	30 min.	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs or more
1. Watching television (including videos on VCR/DVD).	○	○	○	○	○	○	○	○	○
2. Playing computer or video games.	○	○	○	○	○	○	○	○	○
3. Sitting listening to music on the radio, tapes, or CDs.	○	○	○	○	○	○	○	○	○
4. Sitting and talking on the phone.	○	○	○	○	○	○	○	○	○
5. Doing paperwork or computer work (office work, emails, paying bills, etc.)	○	○	○	○	○	○	○	○	○
6. Sitting reading a book or magazine.	○	○	○	○	○	○	○	○	○
7. Playing a musical instrument.	○	○	○	○	○	○	○	○	○
8. Doing artwork or crafts.	○	○	○	○	○	○	○	○	○
9. Sitting and driving in a car, bus, or train.	○	○	○	○	○	○	○	○	○

SEDENTARY BEHAVIOR: Weekend Day

On a typical WEEKEND DAY, how much time do you spend (from when you wake up until you go to bed) doing the following?

	None	**15 min. or less**	**30 min**	**1 hr**	**2 hrs**	**3 hrs**	**4 hrs**	**5 hrs**	**6 hrs or more**
1. Watching television (including videos on VCR/DVD).	○	○	○	○	○	○	○	○	○
2. Playing computer or video games.	○	○	○	○	○	○	○	○	○
3. Sitting listening to music on the radio, tapes, or CDs.	○	○	○	○	○	○	○	○	○
4. Sitting and talking on the phone.	○	○	○	○	○	○	○	○	○
5. Doing paperwork or computer work (office work, emails, paying bills, etc.)	○	○	○	○	○	○	○	○	○
6. Sitting reading a book or magazine.	○	○	○	○	○	○	○	○	○
7. Playing a musical instrument.	○	○	○	○	○	○	○	○	○
8. Doing artwork or crafts.	○	○	○	○	○	○	○	○	○
9. Sitting and driving in a car, bus, or train.	○	○	○	○	○	○	○	○	○