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NATIONAL INCIDENCE STUDY OF INSULIN-DEPENDENT DIABETES MELLITUS IN CHILDHOOD AND ADOLESCENCE IN IRELAND

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A thesis submitted in fulfilment of the requirement

for the award of

DOCTOR IN MEDICINE

The University of Dublin

Trinity College

Dublin

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April 2000

DECLARATION

This thesis is the original work of the investigator with the exception of where acknowledged. It has not been submitted for any degree at this or any other University.

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Signed: Edna T. Rocha

Date: 27th April 2000

TO BRIAN

BECKY

AND

MY MOTHER

EDNA

ACKNOWLEDGEMENTS

I am indebted to a number of people for their help with the work described in this thesis. I would like to express my sincere gratitude to:

Professor Hilary Hoey, my advisor at the Department of Paediatrics, for her advice, guidance, enthusiasm and constant encouragement.

Dr. Chris Patterson, Member of the EURODIABACE Study Group, Department of Epidemiology and Public Health, Queen's University Belfast and the Royal Victoria Hospital, for his kindness, advice and support of this study

Professor Jaako Tuomilehto, European co-ordinator of the World Health Organisation DiaMond Project for his advice and support.

Dr. Jim Kiely, Chief Medical Officer of the Department of Health and Children for his help and support of this study and also Dr. Dominique Crowley, Assistant C.M.O., for her help.

Mr Des Cassidy of the General Medical Services (Payments) Board for his help and support.

Professor Denis Gill and Dr. Anita Menon of the Irish Paediatric Surveillance Unit for supporting this study.

Dr. Myra O'Regan, Department of Statistics, Trinity College, for her advice and support.

I would particularly like to thank the members of the Irish Endocrine Society for their support of this study, the paediatricians and all the adult physicians who participated in this study.

I would like to express my gratitude to Dr. Tom Mitchell, Provost of the University of Dublin, for financial support received from the Provost's Development Fund.

A special word of thanks to Ms Sandra Kenny for administrative support and encouragement throughout this study.

SUMMARY

Type 1 (insulin-dependent) diabetes mellitus is an important chronic medical condition that is associated with significant morbidity and premature mortality. The disease is considered so important that its incidence is deemed a basic health indicator by the World Health Organisation. Studies have shown that optimising medical care for those with diabetes reduces the occurrence of long term disease complications, such as: blindness; kidney failure; and ischaemic heart disease. A prerequisite for maximising medical care for those with diabetes is that information regarding the incidence and characteristics of the disease is available to heath policy makers.

There is wide international variation in the incidence of the diabetes and the highest incidence of the disease is reported in Europe. There is also much evidence that the incidence of diabetes is rising throughout Europe. Little data exists regarding the incidence and characteristics of Type 1 (insulin-dependent) diabetes mellitus in the Irish population. No previous national study has been conducted in Ireland. Two previous studies undertaken in the British Isles included Irish data and found Ireland to have the lowest disease incidence rate in the British Isles and a low rate of disease when compared with other European centres. There was concern that the Irish data in these studies was incomplete resulting in an underestimate of the disease incidence.

This study sought to establish the incidence rate of Type 1 (insulin-dependent) diabetes in Ireland (Republic of Ireland), in those aged under 15 years. It also sought to identify characteristics of the disease in this population, namely; the age of onset; sex; season of onset; infant diet; family history; birth order; number of household occupants; and the clinical course of disease.

A prospective study design was chosen and following national and international consultation, a study protocol was developed and questionnaire designed. Ethical approval for the study was granted by the Joint Ethics Committee of the Federated Dublin Voluntary Hospitals. Following consultation, the Irish Paediatric Surveillance Unit (IPSU) they agreed to support this study and the initial case identification was performed through the mechanism of the IPSU. A monthly reporting card was sent to all paediatricians in the country asking them to notify all new cases of diabetes presenting to them in the study period. Paediatricians who reported cases were sent a questionnaire to complete, to verify the case report and provide additional information. Paediatricians who did not notify cases to the IPSU were contacted to ensure that no cases had been seen. Adult endocrinologists, physicians and all Hospitals nationally were contacted to identify incident cases of diabetes in the study period. The General Medical Services (Payments) Board acted as a second source of case ascertainment through its data relating to the Long-term Illness scheme, which provides insulin and other requirements free of charge to those with diabetes who do not have a medical card. The use of a second source of case identification allowed the

application of the capture-recapture procedure and provided a measure of case ascertainment to the study.

The main results of this study show that Ireland does not have a low incidence of diabetes. The crude incidence rate of the disease in those aged less than 15 years was 16.6 (95% confidence interval 13.9-19.5) per 100,000 per year. This rate reflects the actual disease experience of the population and is important for health policy makers for resource allocation and service provision. The directly standardised incidence rate was 16.3 (14.2-18.5) per 100,000 per year, this rate is constructed for international comparison and shows that Ireland has an incidence rate of diabetes similar to other areas of the British Isles, which are considered high incidence countries. Analysis of incidence data from 44 centres in Europe show that 77% of centres have recorded incidence rates below 15.0 per 100,000 per year confirming that Ireland has a high incidence of diabetes and not a low incidence as previously thought.

There is a slight male preponderance in diabetes in keeping with other high incidence countries. The age of diagnosis is younger in this population, with a mean age of onset of 8.7 years. The peak age at diagnosis is at 8 and 10 years, with a smaller peak at 13-14 years and in early childhood at 3-6 years. The most frequent month of diagnosis is October. The majority of Irish children who develop diabetes do not have a family history of the disease. Presentation is with the classical symptoms of diabetes, namely: polyuria, polydipsia, weight loss and lethargy but not polyphagia. Secondary eneuresis is a particularly important presenting symptom in those aged less than 10 years. 18.6% presented in the life-threatening condition of diabetic ketoacidosis. The majority of children and adolescents in this study had an abrupt onset of clinical diabetes, with symptoms present for only 2 weeks prior to diagnosis. There was a wide range of symptom duration from a few days to 6 months. The duration of symptoms was shortest in the youngest age category and increased with age. This study provides the first baseline measure of diabetes incidence and disease characteristics in this population.

We recommend that policy makers now consider Ireland as a country with a high incidence of insulin-dependent diabetes in future resource allocation and strategic planning decisions relating to diabetes. A Diabetes Register should be established in Ireland to monitor the incidence of this very important disease and establish if a secular trend is present in this population, as in the rest of Europe. A disease register would provide accurate and timely measurement of disease frequency for healthcare provision. It would also provide a mechanism for further epidemiological study with the generation and testing of hypotheses regarding disease aetiology. Significant advances in our understanding of this disease have come from epidemiological studies. A Register would also facilitate comprehensive identification of those at increased risk of disease development, who may wish to avail of diabetes preventative strategies when available.

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CHAPTER ONE

INTRODUCTION

1. INTRODUCTION

Diabetes Mellitus is a chronic medical condition resulting in significant morbidity, disability and premature mortality. Diabetes Mellitus has been described for centuries. It is a disorder where there is an inability to utilise glucose appropriately in the body and so glucose is excreted in the urine. As a result the body constantly loses this energy source which results in wasting of the body in the presence of apparently adequate nutrition. Diabetes is characterised by hyperglycaemia due to defective insulin secretion or resistance to the action of insulin or both. The chronic hyperglycaemia suffered by those with diabetes results in damage to various organs particularly the eyes, kidneys, nerves, heart and blood vessels.

1.1 Classification of Diabetes Mellitus

A number of classifications of diabetes have been proposed. The National Diabetes Data Group (1979) revised the classification of diabetes mellitus which was endorsed by the World Health Organisation (WHO) Expert Committee on Diabetes and the WHO Study group on Diabetes Mellitus (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998). These groups recognised two major types of diabetes mellitus, termed insulin-dependent (IDDM) and non-insulin-dependent (NIDDM), depending on its pharmacological treatment. However, this classification did recognise the heterogeneity of diabetes.

There is a degree of overlap in this classification as it is based on treatment modality and there are patients with non-insulin dependent diabetes who may require insulin therapy. It is also increasingly recognised that there are younger patients who have diabetes mellitus which is not insulin dependent and these are referred to as having Maturity Onset Diabetes of the Young or MODY. Diabetes Mellitus may also occur in pregnancy where it is called gestational diabetes and diabetes may occur as a complication of other medical conditions, such as haemochromatosis or cystic fibrosis.

An international expert committee was established in May 1995, under the sponsorship of the American Diabetes Association, to review the classification and diagnosis of diabetes mellitus. It was proposed to revise the classification of diabetes mellitus towards a system based where possible on disease aeitiology rather than the treatment modality. The report of the expert committee recommended the following classification. (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1998)

In this classification diabetes is divided into four broad types:

I Type 1 Diabetes

Immune Mediated

Idiopathic

II Type 2 Diabetes

III Other Specific Types

Genetic defects of β-cell function, genetic defects of insulin action, diseases of the exocrine pancreas, endocrinopathies, drug or chemical induced, infections, uncommon forms of immune-mediated diabetes eg "stiff-man" syndrome and

anti-insulin receptor antibodies and other genetic syndromes associated with diabetes.

IV Gestational Diabetes Mellitus (GDM)

The terms insulin dependent and non-insulin dependent diabetes are removed from this new classification. In the European literature, the commonly used classification is that of insulin dependent and non-insulin dependent diabetes. However, increasingly both classifications are being used together, that is, Type 1 (insulin-dependent) diabetes.

This study is restricted to the consideration of Type 1(insulin-dependent) diabetes mellitus. This type of Diabetes Mellitus occurs largely in the younger age group. In Type 1 diabetes mellitus there is insulin deficiency and these patients depend on injections of exogenous insulin for their survival. In the absence of treatment this condition rapidly results in death. Prior to the discovery of insulin by Banting and Best in 1921 this disease was universally fatal. Indeed, even in 2000 children with insulin dependent diabetes in developing countries still die due to lack of insulin. In some parts of Africa the life expectancy of a child with newly diagnosed type 1 diabetes may be as little as 1 year (Yudkin, 2000).

Insulin is produced in the body by the β-cells of the pancreas. Insulin acts on target tissues to facilitate the entry of glucose into the cells. Type 1 diabetes is immune mediated or idiopathic in origin. Immune mediated diabetes is due to

cell-mediated autoimmune destruction of the β-cells of the pancreas (Atkinson et al, 1994).

Idiopathic diabetes is a classification for those cases of type 1 diabetes where the aeitiology is unknown. This is the minority and most are of African or Asian origin.

Type 2 Diabetes also known as maturity onset diabetes, is non-insulin dependent and called Non-Insulin Dependent Diabetes (NIDDM). This type of diabetes is more associated with resistance to the action of insulin rather than its absolute absence and is generally treated with dietary manipulations and oral hypoglycaemic agents. Those with non-insulin dependent diabetes tend to be older at disease onset.

1.2 Diagnosis of Diabetes Mellitus

In the majority of children presenting with diabetes the diagnosis is readily apparent. They exhibit the classical symptoms of polyuria, polydipsia and polyphagia. In addition, they also have weight loss despite their increased appetite, fatigue and a number of children with new onset diabetes mellitus may present in diabetic ketoacidosis. These children and adolescents have hyperglycaemia, with blood glucose values generally well above 11.1 mmol/l, and large amounts of glucose and ketones in the urine. Hyperglycaemia in the presence of ketonuria is diagnostic. In these patients there is no difficulty in reaching the diagnosis.

In some situations the diagnosis is less readily apparent and diagnostic criteria have been defined by the World Health Organisation (World Health Organisation, 1985) and further guidelines offered more recently by the American Diabetes Association (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). The diagnosis of diabetes may be made in those presenting with clinical symptoms by either an elevated fasting and 2 hour post-prandial blood glucose value or by two elevated post-prandial levels. The diagnostic blood glucose values have been determined by the World Health Organisation, with a diagostic fasting level of plasma glucose $\geq$ 7.8 mmol/l and two hour post-prandial value $\geq$ 11.1 mmol/l (WHO, 1985).

In 1997 the American Diabetes Association introduced new diagnostic criteria based on fasting plasma glucose alone. In these criteria; a fasting plasma glucose $\geq$ 7.0mmol/l is considered diagnostic. A level of 6.1-7.0mmol/l is considered impaired and a level of fasting plasma glucose $<$ 6.1 is considered normal (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). The purpose of these revised criteria was to simplify the diagnosis of diabetes mellitus and to avoid the need for an oral glucose tolerance test which is rarely required now in clinical practice. A number of studies have been performed to compare the effect of applying the different diagnostic criteria in

diabetes. It is believed that changing the diagnostic criteria, to that based on a lower level of fasting glucose, will lead to earlier diagnosis in those who are destined to develop the disease (Dinneen et al, 1998).

In the absence of significant hyperglycaemia the diagnosis may be made by oral glucose tolerance test. In this test an oral glucose load is given at 1.75g/kg to a maximum of 75g and serial samples of blood and urine are examined for hyperglycaemia, insulin levels and glycosuria.

There are other causes of hyperglycaemia that should be considered in childhood before a diagnosis of diabetes is made on this basis alone. These include the administration of high dose corticosteroids for a variety of conditions, and less frequently tumours of the central nervous system, drugs, phaeochromocytoma and the excessive cortisol produced in adrenal hyperplasia.

1.3 Aetiology of Insulin-Dependent Diabetes

There are genetic influences dictating the predisposition to, or protection from, diabetes which is complex and polygenic. The major histocompatibility complex (MHC) region of chromosome 6, representing HLA antigens, appears to be the most important locus conferring disease susceptibility. However, 15 other provisional

loci have been identified by genome-scale analysis of the genetics of Type 1 diabetes which may also contribute to disease susceptibility (Becker, 1999). The susceptibility genes in the human leucocyte antigens (HLA) relate to the HLA-B8 and B-15 antigens, HLA-DR3 and DR4, and most strongly with HLA-DQ2 and DQ8 alleles. The effect of the latter DQ antigens being modified by the presence of different DR subtypes (Knip, 1998). A further HLA phenotype- HLA-DPB1 has recently been found to confer susceptibility to diabetes, the effect being most pronounced in genotypes other than DR3/DR4-DQB1*0302 (Noble et al, 2000). Over 90% of white type 1 diabetes patients have either a DR3±DR4 antigen compared with only 40% of controls (Becker and Weber, 1995).

Studies in identical twin pairs discordant for IDDM showed that despite genetic identity, diabetes will develop in only 1 in 3 unaffected twin partners (Barnett et al, 1981). This and other studies show that while genetic predisposition to diabetes is important an individuals genetic make-up is not the sole determinant of who will or will not develop diabetes. Indeed, the majority of individuals with the genetic predisposition to diabetes will never develop the disease. In a prospective study of 49 non-diabetic identical twins where the co-twin was recently diagnosed with diabetes, actuarial analysis showed that 34% of twins would be expected to develop diabetes by age 12 and only 2% thereafter

(Olmos et al, 1988). This suggests that up to two thirds of individuals with the genetic predisposition will never develop diabetes.

It would appear that "other factors" are also important in disease development in the genetically predisposed. Evidence exists for an autoimmune process in the destruction of the insulin producing pancreatic β-cells (Atkinson et al, 1994). A variety of antibody markers have been identified which confirm this β-cell destruction, these include: islet cell antibodies (ICAs), insulin autoantibodies (IAAs), autoantibodies to glutamic acid decarboxylase (GAD_{65}) and autoantibodies to tyrosine phosphatases IA-2 and IA-2β (Thai and Eisenbarth, 1993)(Ziegler et al, 1999). One or more of these antibodies are present at diagnosis in 85-90% of individuals. Susceptibility to the development of autoimmune pancreatic destruction is related to specific genotypes, as previously described. Islet Cell antibodies may be produced in low titre in children without the high risk genotype who will not progress to Diabetes but those with the high risk genotype will have progressive pancreatic βcell damage, shown by high titres of ICA (Knip et al, 1998). The initiating or "trigger" event in the development of these pancreatic autoantibodies is unknown. It is thought that this initiating event is environmental. The widely accepted view is that there are "multiple hits" or agents that act on

the genetically predisposed to induce the disease. De Blasio et al (1999), conclude that:

"*onset of type 1 diabetes is due to a collective, dynamic instability, rather than being caused by a single etiological factor.*"

A number of environmental agents have been proposed as potential causative agents of diabetes in the genetically predisposed. These include infectious diseases, environmental toxins, dietary factors and stress.

If environmental exposures in early life are related to the subsequent development of diabetes one would expect to see clustering of cases of diabetes according to time and place of birth. A Swedish study looking for time-space clustering of date at birth in childhood onset diabetes mellitus showed a clustering, according to place and time of birth, for later risk to develop type 1 diabetes. In this study, 198 primary clusters were identified 42 of which, identified three or more patients born in the same area who developed diabetes within two years (Dahlquist and Kallen, 1996). In Iceland, Helgasson and Jonasson (1981) also showed clustering with time for children with diabetes, that is, clustering of birth dates. Clustering in time and space has also been described in the north of England. The effect being most pronounced in the youngest age groups, 0-4 and 5-9 years (Law et al, 1997).

Clustering of cases in this fashion supports the theory that exposure to an environmental agent either pre-natally or early in life may be an initiating event in the subsequent development of Type 1 diabetes. Dahlquist and Kallen's study (1996), did not show variability by months of birth, however, it did show monthly variability between the years. This would again give support to this theory. The proposed environmental exposure is viral infection as the initiating event in the autoimmune process of diabetes development.

Many of the exposures in early life thought related to the subsequent development of diabetes are viral agents. Pre-natal infection with the rubella virus is thought to be strongly associated with the subsequent development of diabetes. A cohort of children followed due to rubella embryopathy had a very high prevalence of diabetes at 30 per cent (Menser et al, 1978). Maternal enteroviral (echo30, coxsackie B5, echo 9) infection during pregnancy was found to be a risk factor for subsequent diabetes in the offspring, the odds ratio being 3.9 (Dahlquist et al, 1995). An increased incidence of insulin dependent diabetes mellitus following an epidemic of Coxsackievirus B5 virus has been described (Wagenknecht et al, 1991). Coxsackievirus B4 virus was cultured from the pancreas at post-mortem examination of a child who died of newly diagnosed diabetes (Yoon et al, 1979). Pak et al (1988), demonstrated evidence of cytomegalovirus in the

peripheral blood of 22% of newly diagnosed patients with diabetes but only in 2.6% of controls.

In addition to naturally acquired infections studies have explored the role of vaccination in disease development. Measles vaccination was found to have a significant effect in reducing the risk of diabetes development (OR = 0.69), or a protective effect. Other vaccinations studied, against tuberculosis, mumps, rubella, pertussis, tetanus and smallpox had no effect (Blom et al, 1991).

However, there is some evidence that exposure to common infections in early childhood may exert a protective effect in those genetically predisposed to diabetes. This has been termed the "hygiene hypothesis" (Kolb and Elliott, 1994). A case control study performed in the United Kingdom by Gibbon et al (1997), demonstrated that infections had a protective effect during the first year of life (OR 0.81 per infective episode) but not for the remaining four years under study.

There is convincing evidence to support the role of an, as yet, unidentified infectious agent as an initiator in the development of diabetes. However, this role has not been fully elucidated. Direct examination of pancreatic samples in children who died following newly diagnosed diabetes failed to show evidence of Ebstein–Barr, cytomegalovirus, coxsackievirus or mumps virus (Foulis et al,

1997). These four viruses are considered the most likely viral candidates from studies to date. It is possible that another viral agent, such as a retrovirus, may be the infectious promoting agent in diabetes (Foulis et al, 1997).

Certain environmental toxins have been implicated in the development of diabetes. Streptozotocin has been used to induce diabetes in laboratory animals and also to destroy the pancreas in humans with islet cell malignancy (Becker and Weber, 1995). Nitrosamines in food have been implicated as a potential cause of diabetes. These agents are produced when food is cured by smoking. An association with increased levels of nitrates in drinking water and a higher incidence of diabetes was found in the north of England (Parslow et al, 1997). It is likely that there are other toxic agents entering the food chain in developed countries that are as yet unidentified. Other dietary factors, such as cow's milk, are also thought to be important in the development of diabetes and this will be discussed in section 1.8 (page 37).

The stress response of the body through activation of the hypothalamic-pituitary-adrenal axis, releasing adrenocorticotrophic hormone and adrenal steroids, has been shown to reduce the effectiveness of the immunological surveillance system (Becker and Weber, 1995). This supports a role for acute emotional stress

in the precipitation of diabetes which has been described in some studies (Danowski, 1963; Thernlund et al, 1995; Carter et al, 1987 and Hagglof et al, 1991).

1.4 Incidence of Insulin-Dependent Diabetes Mellitus

Type 1 (insulin dependent) diabetes mellitus is one of the most important chronic medical conditions of children and adolescents worldwide. The World Health Organisation (WHO), has recognised the importance of this disease by stating that the incidence of this disease should be considered a basic health indicator on a national basis. In further recognition of the importance of this disease and its burden on individuals and healthcare providers the World Health Organisation has established a multinational project on childhood diabetes to investigate and monitor the international patterns of IDDM incidence to the year 2000. This project, the DIAMOND project, has as its primary goal the collection of accurate population based information on the incidence of insulin dependent diabetes. The study plans to collect population data on diabetes in more than 90 centres in 50 countries worldwide, over a 10 year period from 1990 to 1999 (WHO Diamond project group, 1990).

Prior to this the Diabetes Epidemiology Research International Group (DERI), initiated the collection of standardised data between the late 1970s to mid 1980s (Karoven et al, 1993).

The benefits of this and similar projects is that a standardised case definition and measures of ascertainment are included in the methodology which facilitates valid comparison in incidence rates between countries and over time. Previous studies, such as, that by Bloom et al (1975), in the British Isles do not give a measure of ascertainment which makes comparison with other studies difficult.

1.4.1 World-wide Incidence of Insulin Dependent Diabetes

The incidence of Diabetes Mellitus in childhood is subject to wide geographical variation. The DERI Group published the first standardised incidence rates as a result of international collaboration between 24 registries in 15 countries. This showed that during the years 1978 to 1980, the average annual age-adjusted incidence under 15 years, ranged from 1.7 per 100,000 per year in Hokkaido, Japan to 29.5 per 100,000 per year in Finland (DERI Group, 1988).

More recent studies have demonstrated an annual incidence rate of diabetes from 0.6 per 100,000 per year in Korea and Mexico City

to 35.3 per 100,000 per year in Finland (1987-9) (Karoven et al, 1993). A recent study in China reports the lowest reported incidence in the world, in children under the age of 15, at 0.51 per 100,000 per year (Yang Ze et al, 1998).

There is a marked difference in the incidence of diabetes between southern and northern hemispheres. No country below the equator has a recorded incidence above 20 per 100,000. However, a simple north-south gradient does not explain the differences noted in the incidence of the disease.

The highest incidences are found in Europe. The lowest incidence of diabetes is found in Asia, with incidence rates reported at: 1.63 per 100,000 per year in Hokkaido, Japan (Matsuura et al, 1998); 4.6 per 100,000 per year in Novosibirsk, Russia; 0.6 per 100,000 per year in Korea (Karoven et al, 1993); and 0.51 per 100,000 per year in China (Yang Ze et al, 1998).

The incidence in Australia has been reported as 13.2 per 100,000 per year, based on a 1985-89 study in western Australia and New Zealand (Canterbury) reported an incidence of 11.6 per 100,000 per year in 1981-86 (Karoven et al, 1993). Incidence rates for South America include low incidence rates, of: 7.6 in Brazil; 2.5 in Chile; and 1.0 per 100,000 per year in Peru. In North America, incidence rates range from: 23.9 in Prince Edward Island, Canada;

20.4 in Manitoba, Canada (Blanchard et al, 1997); and 9.8 in Montreal; to 0.6 per 100,000 per year in Mexico City (Rewers et al, 1988). The United States reported incidence rates of 18.2 in Wisconsin, and in Allegheny County a rate of 17.3 in Whites and 11.5 in non-Whites. In the Colorado study an incidence rate of 15.5 in non-Hispanics and 8.8 in Hispanics was reported (Kostraba et al, 1992). The incidence in Jefferson County, Alabama, was reported as 15.6 per 100,000 per year (Wegenknecht et al, 1989).

There is little data relating to the incidence of diabetes in Africa. Reported incidence rates are: 6.4 in Khartoum, Sudan (Elamin et al, 1992); 1.5 per 100,000 per year aged 0-19 years in Dar es Salaam, Tanzania; (Swai et al, 1993); and 8.1per 100,000 per year in Oran, Algeria (Karoven et al, 1993). No measure of ascertainment is given in the studies from Algeria or Tanzania.

Thus, a wide geographical variation exists in the incidence of Type1 (insulin dependent) diabetes world-wide.

1.4.2 Incidence of Insulin-Dependent Diabetes in Europe

The highest incidence of Type 1 (insulin-dependent) diabetes is found in Europe and people of European descent. The widest intercontinental variation also occurs in Europe with the lowest areas being Northern Greece at 4.6 and Macedonia at 2.45 per 100,000 per year (Kocova et al, 1993), and the highest incidence in Finland at 35.3 in 1987-1989 (Tuomilehto et al, 1992). A further study, in 1989-1990, of 2 regions in Finland showed an even higher incidence rate of 42.9 per 100,000 (Green et al, 1992). Finland has the highest incidence of Diabetes in the world followed by an unexpected high incidence in Sardinia, which has the second highest rate in Europe, at 30.2 per 100,000 per year. Scandinavian countries also have very high rates. Eastern Europe generally had low rates with Macedonia, formerly part of Yugoslavia, having a particularly low incidence of diabetes.

EURODIAB ACE is a collaborative European study (1989-90), established to assess the incidence of childhood insulin dependent diabetes in Europe, it later included Israel. This study showed a very significant variation in the incidence of diabetes in Europe with a 10 fold variation between the lowest rate in Northern Greece(4.6) and the highest rate in Finland (42.9). When data from Macedonia is considered there is a 20-fold variation in diabetes incidence throughout Europe. The wide variation in diabetes incidence in Europe in 1989-90 is shown in Table 1.1 page 18.

Table 1.1

Standardised Incidence Rates of Insulin Dependent Diabetes aged 0-14 years in Europe (1989/90)

Country (region)	Boys Rate* (95% C.L.)	Girls Rate* (95% C.L.)	All Rate* (95% C.L.)
Greece (Northern)	5.3(2.4,10.1)	3.8(1.4,8.2)	4.6 (2.6,7.5)
Romania (Bucharest region)	4.6(2.9,6.9)	5.7(3.7,8.4)	5.1 (3.8,6.8)
Poland (9 western provinces)	5.3(4.6,6.5)	5.8(4.6,7.2)	5.5 (4.7,6.4)
Israel (whole nation)	4.4(3.4,5.6)	6.7(5.4,8.2)	5.5 (4.7,6.5)
Poland (3 cities)	5.7(4.2,7.5)	6.0(4.5,7.9)	5.8(4.8,7.1)
Slovenia	5.2(3.3,10.4)	7.7(5.3,10.9)	6.5(4.9,8.4)
Italy (Lazio region)	7.2(5.5,9.1)	5.8(4.4,7.7)	6.5(5.4,7.8)
Italy (Lombardia region)	7.6(6.3,9.2)	5.9(4.7,7.3)	6.8(5.8,7.8)
Portugal (3 regions combined)	10.1(5.9,16.1)	4.9(2.1,9.6)	7.5 (4.8,11.0)
Hungary (18 counties)	7.7(6.4,9.1)	7.5(6.3,9.0)	7.6(6.7,8.6)
Austria(whole nation)	7.9(6.5,9.3)	7.5(6.1,9.2)	7.7 (6.7,7.8)
France (4 regions)	7.8(6.6,9.3)	7.8(6.5,9.2)	7.8 (6.9,8.8)
Greece(Athens region)	10.9(8.5,13.7)	7.7(5.7,10.2)	9.3(7.7,11.1)
Belgium (Antwerp region)	9.2 (5.2, 15.3)	10.4 (5.9,16.9)	9.8 (6.7, 13.9)
Italy (eastern Sicily)	11.2(7.5,16.1)	9.0(5.7,13.5)	10.1(7.5,13.2)
Spain (Catalonia region)	10.5(8.8,12.3)	10.6(9.0,12.5)	10.6(9.4,11.9)
Netherlands (5 regions)	11.2(7.6, 16.0)	10.8(7.2,15.7)	11.0(8.4,11.3)
Luxembourg (whole nation)	12.1(5.2,23.9)	12.6(5.4,24.8)	12.4(7.1,20.1)
UK (Oxford region)	17.8(14.3,21.9)	14.9(11.7,18.8)	16.4(13.9,19.1)
UK (Northern Ireland)	17.8(13.9,22.5)	15.4(11.7,19.8)	16.6(13.9,19.7)
Norway (8 counties)	22.3(17.9,27.6)	19.3(15.1,24.3)	20.8(17.7,24.3)
Denmark (3 counties)	21.5(14.9,30.1)	21.4(14.7,30.3)	21.5(16.6, 7.3)
Italy (Sardinia)	33.5(27.9,39.9)	26.9(21.7,32.9)	30.2(26.4,34.4)
Finland (2 regions)	47.0 (37.5,58.1)	38.8(30.5,50.0)	42.9(36.3,50.6)

*number of cases per 100,000per year

Derived from EURODIAB ACE data *Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE study – A.Green, EAM Gale, CC Patterson, The Lancet Vol 339 April, 1992, 905-909.*

A more recent report from the EURODIAB ACE Study Group (2000), confirms this wide variation in disease incidence in Europe. This report is based on disease incidence in the period 1989-94, it confirms the lowest European disease incidence in Macedonia at 3.2 cases per 100,000 per year and the highest in 2 regions of Finland at 40.2 cases per 100,000 per year (Table 1.2 Page 20).

The incidence of diabetes tends to be higher in northern countries but the distribution does not reflect a simple north south gradient. Sardinia despite its southern position has a high rate and Iceland,(reported incidence rate for Iceland was 9.4 (Helgasson et al, 1992)) in the north has a lower rate similar to that of Sicily and Spain. Scandinavia and United Kingdom do have higher rates than the rest of Europe in keeping with their northern positions.

Table 1.2 Standardised incidence rates of insulin-dependent diabetes aged 0-14 years in Europe (1989-94)

Country	Region	Standardised incidence rate per 100,000 (95%CI)	Study Period
Austria	Whole Nation	9.1(8.5-9.8)	1991-94
Belgium	Antwerp	11.6(9.4-13.7)	1989-94
Bulgaria	Western	9.6(8.5-10.7)	1989-94
	Eastern	6.8(5.9-7.7)	1989 - 94
Croatia	Zagreb	6.8(5.3-8.3)	1989-94
Czech Republic	Whole nation	8.9(8.3-9.4)	1989-94
Denmark	4 counties	16.0(13.9-18.1)	1991-94
Estonia	Whole Nation	10.3(8.9-11.7)	1989-94
Finland	2 regions	40.2(36.4-44.1)	1992-93
France	4 regions	8.3(7.8-8.9)	1991-94
Germany	Dusseldorf	14.0(11.4-16.6)	1993-94
	Baden-Wurttemberg	11.3(10.6-12.0)	1989-94
Greece	Attica	9.5(8.5-10.5)	1993-94
	5 northern regions	6.2(4.5-8.0)	1989-94
Hungary	18 counties	8.9(8.2-9.5)	1989-94
Iceland	Whole nation	13.5(9.8-17.2)	1989-94
Italy	Lombardia	7.0(6.4-7.6)	
	Lazio	8.1(7.3-8.9)	1993-94
	Sardinia	36.6(33.9-39.4)	1991-94
	Eastern Sicily	11.4(9.5-13.2)	1991-94
Latvia	Whole nation	6.6(5.8-7.5)	1993-94
Lithuania	Whole nation	7.4(6.6-8.1)	1989-94
Luxembourg	Whole nation	12.1(8.7-15.5)	1993-94
Macedonia	Whole nation	3.2(2.5-3.8)	1989-94
Netherlands	5 regions	13.0(11.8-14.3)	1991-94
Norway	8 counties	21.2(19.3-23.1)	1992-94
Poland	8 western provinces	6.7(6.2-7.3)	1991-94
	3 cities	6.1(5.4-6.8)	1989-94
	Gliwice	5.4(4.8-6.0)	
	Bialystok	5.5(3.5-7.4)	1994
Portugal	Madeira	6.9(4.1-9.6)	1993-94
	Portalegre	19.0(11.5-26.5)	1989-94
	Algarve	13.6(9.8-17.3)	1991-94
Romania	Bucharest	5.0(4.1-5.8)	1989-94
Slovakia	Whole nation	8.4(7.7-9.0)	1989-94
Slovenia	Whole nation	7.6(6.5-8.7)	1992-94
Spain	Catalonia	12.3(11.4-13.1)	1991-94
Sweden	Stockholm county	25.8(23.4-28.2)	1993-94
Switzerland	Whole nation	7.9(7.1-8.7)	
United Kingdom	Northern Ireland	19.6(17.8-21.4)	1989-94
	Oxford	17.6(16.1-19.1)	
	Leicester	15.9(13.5-18.3)	1989-93
	Leeds	15.7(14.5-16.9)	1989-94

Table constructed from data in Variation and trends in incidence of childhood Diabetes in Europe, EURODIAB ACE Study Group, Lancet 2000; 355: 873-6.

1.4.3 Incidence of Insulin-Dependent Diabetes in the British Isles

In 1972 the British Diabetic Association sponsored a register of newly diagnosed diabetes, in those aged 0-15 years, in Great Britain and Ireland. In this study the overall yearly incidence of diabetes was calculated to be 7.67 per 100,000 per year. Variation in incidence was noted in different geographic areas with notably fewer cases reported in Greater London and Ireland. In 1973, only 51 cases were notified from Ireland equivalent to 4.43 notification per 100,000 and 58 cases in 1974 equivalent to 5.17 notifications per 100,000. No measure of ascertainment was provided in this study (Bloom et al, 1975).

A further study of the incidence of Type 1 (insulin dependent) diabetes in children under 15 years in the British Isles during 1988, by Metcalfe and Baum (1991), gave an overall incidence rate of 13.5 per 100,000 per year (95% 12.9 – 14.2). This study showed an unusual geographical variation in incidence. The lowest incidence rate was recorded for Ireland at 6.8 per 100,000 per year and the highest rate for Scotland at 19.8 per 100,000 per year. Ascertainment in this study was considered to be about 90%. However, ascertainment data was presented for England and Wales only. No measure of case ascertainment is provided in this study for Ireland.

The Yorkshire Diabetes Register calculated an incidence rate of 13.7 per 100,000 per year between 1978 and 1990. The completeness of ascertainment was 97.6% (Staines et al, 1993). Bingley and Gale (1989a) found the incidence in the Oxford region to be 16.4 per 100,000 (95% confidence interval 13.9-19.1) and that in Northern Ireland 16.6 per 100,000 per year (95% confidence interval 13.9-19.7) (Green et al, 1992). The incidence in Northern Ireland was noted to be 19.6 per 100,000 per year (95% confidence interval 17.8-21.4) and that in Leeds, 15.7 per 100,000 per year (95% confidence interval 14.5-16.9) in the period 1989-1994 (EURODIAB ACE, 2000).

Patterson et al (1983) calculated the incidence in Scotland as 18 per 100,000 per year in those under 19 years in 1976. While there has been some criticism of the methodology employed in this study subsequent studies have supported the finding that Scotland has the highest incidence of diabetes in the British Isles. A subsequent study in Scottish children between 1984 and 1993 found the average annual incidence rate to be 23.9 per 100,000 in those under 15 years. It also documented increasing incidence with age (Rangasami et al, 1997).

Thus even within the small land mass of the British Isles significant variation in the incidence of diabetes has been described. The two studies of diabetes incidence that included the

Irish population both found fewer case notifications from Ireland and reported a lower disease incidence. However, as neither of these studies provided a measure of ascertainment their findings could reflect under ascertainment of cases rather than a true reduction in the incidence of diabetes in the Irish population. No ascertainment validated data is currently available for the incidence of diabetes in Ireland.

1.4.4 Migrant Studies

There is wide geographical variation in the incidence of Type 1 diabetes. The incidence of diabetes is highest in Europeans and those of European descent. The incidence is lower in Asian populations and in those of African origin. In countries that have sub-populations of different ethnic origins varying incidence rates of diabetes have been reported for these different ethnic groups.

In the United Kingdom, the incidence of diabetes in Asian children rose from 3.1 per 100,000 per year, in the period 1978-81, to 11.7 per 100,000 per year, in 1988-90. The rate for other children in the area remained constant over this time at 10.5 per 100,000 per year (Bodansky et al, 1992). In this population the incidence of diabetes in Asian immigrants was rising to approach that of the indigenous population

Reports in Jefferson County, Alabama (United States) indicate a modest reduction in risk among African Americans, who have an incidence rate of 12.1 per 100,000 per year, while the corresponding incidence rate in the White population is 15.6 per 100,000 per year (Wagenknecht et al, 1989). In Allegheny county, Pennsylvania, the incidence rate for the non-white population was significantly lower at 11.5 per 100,000 per year while that in the white population was 17.3 per 100,000 per year (Rewers et al, 1989). In Barbados, where 90% of the population is of West African origin, the adjusted incidence rate was 5.0 per 100,000 per year for those under 15 years of age (Jordan et al, 1994). This is significantly lower than the incidence rates recorded for those of African origin living in the United States.

The incidence of Type 1 (insulin-dependent) diabetes in children living in Puerto Rico was recorded as 18 per 100,000 per year(95% CI 17.6-18.3) which is high for a low latitude country (Frazer de Llado et al, 1998). Two previous studies that included Puerto Rican populations living in the United States both reported a higher incidence than in US Caucasians at 15-18 per 100,000 per year, which is the same as the incidence in Puerto Rico (Lipman et al, 1993 and Lipton et al, 1995). However, a study of Hispanic children living in Colorado, demonstrated an incidence rate of 8.7 per 100,000 per year which was much lower than that noted in non-Hispanics at 15.5 per 100,000 per year. This is significantly lower

than the incidence rate in those living in Puerto Rico and perhaps relates to under-ascertainment in this population rather than a true reduction in incidence (Kostraba et al, 1992).

Marked ethnic variation in incidence rates in different ethnic groups has also been described in China. A six-fold difference in incidence has been reported among different ethnic groups, the highest incidence was in Mongols at 1.82 per 100,000 per year and the lowest in Zhuang at 0.32 per 100,000 per year (Yang Ze et al, 1988).

In Montreal there has been approximately a doubling of incidence among children of French, Israeli, and Italian origin living in Montreal compared to that of their native country (Siemaitycki et al, 1988). The incidence of diabetes in the immigrant populations was rising to approach that of the indigenous population. Such findings strongly support the role of environmental agents in the development of diabetes in the genetically predisposed.

A criticism of these migrant studies in proving an environmental effect, is that the incidence of diabetes has not been shown to fall when migration is from an area of high incidence to one of low incidence. However, the patterns of migration in large numbers tend to be from areas of low incidence to those of high incidence, such as migration from Asia or Africa to Europe or North America.

There may be evidence of reduction in incidence in Iceland which has an incidence rate half that of Norway from where the founders of Iceland emigrated (Green et al, 1992).

An interesting study has been performed on children of Sardinian heritage migrating to Lazio. These two areas of Italy have very different incidence rates of diabetes with Sardinia having an unusually high incidence of the disease for its geographical position, the second highest in Europe. The age adjusted incidence of diabetes in Sardinian heritage children born and living in Lazio was 33.8 per 100,000 per year (95 % confidence interval 7.0-99.0) for those with two Sardinian parents. The rate was almost half at 15.9 per 100,000 per year (8.7-26.6) for those with one Sardinian parent. The incidence in Sardinia was 34.4 per 100,000 per year (31.3-37.9) and was four times that of Lazio heritage children at 7.9 (7.1- 8.8). Children of Sardinian heritage born in Lazio showed the same incidence as the population of origin. Children with one Sardinian parent had a rate half that of Sardinians and double that of the indigenous population. This study did not show any reduction in risk with migration to a low incidence country. This is interesting when compared to the findings of the above studies which have shown migrating children to approach the incidence rate of the new country (Muntoni et al, 1997).

However, the experience of Sardinian heritage children, born in nearby low incidence Lazio, show a pattern of risk that is more suggestive of a strong genetic rather than environmental effect.

1.4.5 Secular Trends in the Incidence of Diabetes

A large number of studies internationally have suggested a rising incidence of diabetes in the last 20-30 years. Many of the earlier studies employed differing methodologies or did not provide any measure of ascertainment and so comparison is of limited value. The concern being that improved case ascertainment could lead to an apparent increase in incidence when no real effect exists.

The DERI Group sought to evaluate trends in the incidence of diabetes over a 21 year time period (1966 – 1986). The use of standardised methodologies by the DERI Group facilitates comparison. The DERI study confirmed a linear increase in Type 1 (insulin dependent) diabetes risk for those under 15 years of age in most of Europe and the Western Pacific but not in North America (D.E.R.I. Group, 1990). The US data only related to two areas where there was a long period of observation. The incidence in Montreal was stable until the 1980's and then rose. Evidence of linear increase in risk was found in Finland, Sweden, Norway, Austria and Wielkopolska (Poland), that did not differ for age group. In Leicestershire (UK), there was also linear increase in risk but this

differed for the three age groups: 0-4, 5-9 and 10-14 years. The steepest increase being in the youngest age group. In Vasterbotten there was non-linear variability which differed for the three groups. Studies from Finland report a 57% increase in a 20 year period, from 1965 to 1984 (Tuomilehto et al, 1991).

There was no evidence for a temporal change in Scotland in the D.E.R.I. study. Patterson et al (1983), did report an 80% increase in incidence in Scotland in the period 1968-76, from approximately 10 in 1968 to 18.3 per 100,000 per year in 1976. This study was based on hospital admission data. The authors applied a correction factor to select incident cases from re-admissions, however, a potential for error remains with this methodology. A subsequent study in Scotland by Rangasami et al (1997), for the period 1984 to 1993 confirmed a rising incidence in Scotland with a rate of increase calculated at 2% per annum. The incidence rose from 22.7 (95% CI 19.8-25.6) in 1984 to 26.0 per 100,000 per year (95% CI 23.3-28.7) in 1993.

The incidence in Yorkshire, Great Britain was also shown to be steadily increasing with evidence of a modest drift effect of 1.75 % per-year (95 % confidence interval 0.28 to 3.25 %). This would equate with a doubling of disease incidence in 40 years. A marked epidemic pattern was evident with peaks at four-year intervals (Staines et al, 1993).

The recent report from the EURODIAB ACE Study Group (2000) relating to incidence data collected from 44 centres in Europe (43) and Israel, in the period 1989-1994, demonstrates that the incidence of diabetes continues to increase in

Europe. Of the 40 centres included in this analysis all but one showed an increased incidence rate. The annual rate of increase in incidence was 3.4% (95% confidence interval 2.5-4.4%). The increase in incidence was noted to vary from country to country (see Tables 1.1 page 27 and 1.2 page 28). A greater relative increase in incidence was demonstrated in those under 5 years of age. No reliable data exists for Ireland regarding temporal trends in diabetes.

Bingley and Gale (1989), concluded that there had been an increased incidence in Type 1 (insulin dependent) diabetes in Northern Europe which had been steady and sustained for more than 20 years. The incidence rate having doubled in a number of countries in this time period. The more recent studies cited above show that this trend of increasing incidence in diabetes is continuing.

1.4.6 Epidemics of Diabetes

In addition to noting a gradual increase in incidence in diabetes several areas have reported "epidemics" of diabetes, where there have been significant increases in incidence over a short period of time. This effect has been noted in Allegheny County, Pennsylvania. In this area the incidence of diabetes had been relatively stable over a 20-year period, from 1965 to 1985, ranging from 11.5 to 13.9 per 100,000 per year. However, in the period 1985 to 1989, the incidence rose sharply to 17.1 (95% CI 15.2-19.2). There was a large increase in the youngest age group, 0-4 years. The largest increase was noted in non-white males (Tomadher and Dokheel, 1993). This is strongly suggestive of an environmental infectious

aeitiology. An association was noted with an increased number of reported cases of chickenpox 2-3 years earlier.

A similar phenomenon was reported in Midwestern Poland where the incidence of diabetes was noted to almost double from 3.5 per 100,000 per year, in 1970-1981, to 6.6 per 100,000 per year, in 1982-1984. This increase was again noted most significantly in boys in the younger, 0-4 year age group (Rewers et al, 1987).

1.5 Age of Onset

There is some evidence that the age of diagnosis of insulin dependent diabetes is genetically determined. A study performed by Caillat-Zucman et al (1992), shows that patients diagnosed in childhood are more likely to have the HLA genes associated with susceptibility to diabetes than those diagnosed as adults, namely HLA DR 3 / 4 and HLADQA1 0301- DQB1 0302. Further support for the genetic basis of the age of diagnoses of diabetes comes from twin studies. Twins concordant for diabetes tend to be diagnosed within a few years of each other and the risk of developing diabetes in a second twin declines with time (Olmos et al, 1998). A study by Danla Fava et al (1998), sought to explore the relationship of genetic and environmental factors on the age of diagnosis of diabetes. They studied twin pairs concordant for type 1 diabetes and pairs of affected siblings. If environmental factors were most influential for dictating age at diagnosis one would expect to find siblings with diabetes diagnosed at a similar time. If however, genetic factors have a greater role to play the expectation is that siblings would be diagnosed with diabetes at a similar age. Fava's study shows a strong correlation in identical twin pairs for their age of

onset of diabetes. In the study both identical and non-identical twins showed a strong correlation for age of onset but this correlation is stronger for identical twins at 0.96 versus 0.59. " This data implies that genetic factors influence the rate of progression of the destructive process during the pre-diabetic period." There was also found to be a correlation between siblings for the age but not the time of diagnosis of diabetes. The authors suggest that since certain HLA types are found more often in those diagnosed in childhood rather than adult life perhaps, the diabetic disease process is more aggressive in those with certain HLA and non-HLA genes.

In several studies the age of onset of diabetes has been shown to have a bimodal distribution. Sterkey et al (1978), described a peak onset at 12 years with a smaller peak at about seven years in Swedish children. The boys had a peak incidence at 7 and 13 years respectively and the girls a less pronounced a peak at 10 years of age. The mean age of onset for both sexes combined was 8.2 years. There was a dramatic fall in incidence at 14 years of age. A similar bimodal distribution was noted in the British Isles by Bloom et al (1975), with a peak onset at approximately 11 years and a second peak at about five years. Bloom similarly showed a dramatic fall in incidence in the adolescent years with a sharp fall in incidence after age 11/12, more obvious in girls than boys. The adolescent fall in incidence was earlier in this study. A further study in the United Kingdom by Staines et al (1993), again showed two peaks in age of onset in this population at age 4-6 and age 10-15 years. The peak incidence in girls was earlier than that in boys at 10 and 14 years respectively, while in children under 7 years the mean age of onset was almost identical. A bimodal distribution

was also reported in Scotland with a peak for boys at 11 years and another smaller peak at 3 years. In girls the peak onset was noted to be later, which is at variance with the majority of other studies noted above, at 12 years with a smaller peak at 4 years (Patterson et al, 1983). A bimodal distribution has also been reported in Japan (Matsuura et al, 1998), mid-west Poland (Wielkopolska) (Rewers et al, 1987) and Hungary (Soltesz et al, 1990).

It has been proposed that the bimodal distribution may relate to the age of starting school and the age of changing to second level school which occur at age 5 and age 11 years in the U.K.(Bloom et al, 1975). The earlier onset in girls in adolescence has been postulated to relate to the earlier timing of the female growth spurt (Staines et al, 1993).

In Sweden, Dahlquist et al (1982), showed a gradual increase throughout childhood with a peak incidence at 11 years for girls and a bimodal distribution for boys with peak onset at age 4 and 13 years.

A monomodal distribution has been reported in Finland and in the British Isles. In the British Isles, a rising incidence throughout childhood was noted in both sexes with a peak age of onset for girls at about 12 years (mean 12.2) and for boys between 12 and 13 years (mean 12.6) (Metcalfe and Baum, 1991). In Finland, the mean annual incidence rose throughout childhood and peaked in girls at 12 years and boys at 14 years with an abrupt decline after these respective ages (Reunanen et al, 1982 and Tuomilehto et al, 1991). A similar pattern in age distribution has been reported in Norwegian children, by Joner et

al (1981), with rising values throughout childhood to a peak at 12 years for girls and a plateau at 12-14 years for boys. An abrupt decline was noted after 12 years in girls and after 14 years in boys.

In the Marche region of Italy, the highest incidence rates were noted for children in the five to nine age group (Cherubini et al, 1994). This pattern has also been reported in other areas of Italy, but throughout Europe the peak has appeared in the 10-14 age group and the incidence rates were lowest in the 0-4 age group (Green et al, 1992).

1.6 Sex

Diabetes often shows a slight male preponderance in Caucasians. Africans and Asians often show a higher incidence in females (Rewers et al, 1988).

In the EURODIAB ACE study, a small excess of male cases was noted but it did not reach statistical significance. However, the results suggested a slight male excess in some areas with high incidence such as Finland, Sardinia and Norway (Green et al, 1992). This is also true for the British Isles and Austria. Bloom et al (1975), in the British Isles showed a slight male excess in the age groups 0-4 and 11-15 years, and a female excess from 5-10 years. Norway, a high incidence country (overall mean annual incidence 17.6) showed a significantly higher incidence in boys at 18.8 than girls at 16.4 per 100,000 per year (Joner et al, 1981).

The areas of low incidence showed a slight female excess in areas such as Romania, Israel, and Poland (Green et al, 1992). This is also true for Hungary, Lithuania, Latvia and Japan (Soltesz et al, 1992). In Hokkaido Japan, a significantly higher annual incidence was documented in females at 1.81 per 100,000 per year than in males at 1.45 per 100,000 per year (Matsuura et al, 1998). In Puerto Rico a slight female preponderance was shown, with a male to female ratio of 0.91 (Frazer de Llado et al, 1998).

No significant sex related difference in incidence was noted in the Marche region, Italy (Cherubini et al, 1994), Sweden (Sterkey et al, 1978), Iceland (Helgason et al, 1992), Catalonia (Goday et al, 1992) and Colorado (Hamman et al, 1990).

1.7 Season of Onset of Diabetes

The finding of a seasonal pattern in a disease is important as it may give clues as to the underlying aeitiology. Seasonality is often found in diseases that are caused by infection. Adams (1926) showed a seasonal pattern in his study of diabetes in Minnesota. The peak incidence was noted in September and the lowest incidence in May and June. Gamble and Taylor (1969) described the lowest incidence in June with an increase in early summer to a peak in October.

Seasonality was also described in Norway, with more cases diagnosed in winter and autumn with significant peaks in February and October (Joner and Sovik, 1981). A significant seasonal pattern was noted for the sexes combined and for the age groups 0-9 and 10-14 years in Finland. A statistically significant pattern was confirmed for males but not for females. The most visible seasonal pattern was a lower number of cases in June. The rest of the year the incidence was stable and high (Karoven et al, 1996). Seasonal patterns have also been described for Sweden with a peak incidence in January, March and July to October for age groups 5-9 and 10-14 years. No seasonal variation was noted for younger children aged 0-4 years (Dahlquist et al, 1982). An earlier Swedish study showed no significant seasonal variation. However, there was a high frequency of new cases in January, that did reach statistical significance and a tendency to a smaller peak in September/October (Sterky et al, 1978).

Seasonal variation in incidence has also been described in the British Isles in older children but most studies show no seasonal effect in those under 5 years of age. Bloom et al (1975), demonstrated seasonal variation in incidence in children aged five to 15 years with peaks in the autumn and winter and a nadir in June and July. Those under 5 years of age showed no obvious seasonal pattern. A further study in Yorkshire confirmed this seasonality, again confined to those over five years of age. Season variation being most pronounced in those aged 10-16 years with mild seasonal variation noted in the 5 – 9 year age group. The peak incidence was in winter (χ^2=48.24;df=2; p<0.0001). There was no difference in the pattern of seasonal onset between boys and girls (Staines et al, 1993). In Scotland a significant seasonal effect was found for both sexes but again only for

the older age groups. The peak incidence was found in Autumn/Winter (Rangasami et al, 1997). Metcalfe and Baum (1991), demonstrated a significant seasonal effect in their study in the British Isles in all three age groups but the effect was less pronounced in the 10-14 year age group. The majority of cases were diagnosed in February and March and the lowest numbers in May and June.

In Puerto Rico there was no significant difference in the number of cases diagnosed in summer or winter although there was a slight increase in winter (Frazer de Llado et al, 1998).

In Malta the highest incidence was noted during the coolest months of the year and the lowest during the summer months. This was seen in both sexes. There was a slight shift in the peak time that is from November to February in the 1980s and January to April in the 1990s (Schranz, 1998). Similarly, in Italy (Marche region) there was a slight but not significant increase in newly diagnosed children in the colder months (October to February) of the year (Cherubini, 1994). Macedonia noted seasonality with the majority of cases in fall-winter and the lowest in Summer (Kocova et al, 1993). Seasonal variation has also been reported in Japan (Matsuura et al,1998), Catalonia (Goday et al, 1992) and Colorado (Kostraba et al, 1992). In Colorado no significant seasonal pattern was noted in those diagnosed before the age of 5 years.

Seasonal variation was not noted in Sardinia (Tuomilehto et al, 1992).

The majority of studies have demonstrated a seasonal effect in the clinical onset of disease. However, many of the studies outlined above have not demonstrated this effect in the younger, 0-5 year, age group. It was considered that in individual registries the number of cases in this age group could be too small to demonstrate a seasonal effect when considered individually. The EURODIAB ACE Study group sought to clarify the issue of seasonality by examining data from 26 centres (Levy-Marchal et al, 1995). They confirmed that seasonality of diagnosis conformed to a sinusoidal model with a peak occurring in winter. This was observed in both sexes and in all age groups. A statistically significant heterogeneity in seasonal distribution was noted among regions, those in Scandinavia showing the lowest relative amplitude. In eleven centres the test for seasonality reached statistical significance and in these the peak months of diagnosis were: November (1), December (3), January (4), February (2) and March (1).

1.8 Infant Diet

Infant feeding practices have received much attention as potential initiating factors in the development of type 1 diabetes, as described in section 1.4. Early breast feeding practices and early exposure to cow's milk are considered the most significant dietary factors and are the subject of much research (Borch-Johnson et al, 1984) (Verge et al, 1994) (Gerstein et al, 1994).

Increased levels of cow's milk and β-lactoglobulin antibodies have been detected in young children with newly diagnosed type 1 diabetes indicating a strong humoral response to cow's milk protein. It is postulated that the autoimmune process could be initiated by cow's milk derived peptides through molecular mimicry of surface membranes of pancreatic β-cells (Savilahti et al, 1993). Increased levels of antibodies to bovine serum albumin, another milk protein, were also found in diabetic children compared to controls (Saukkonen et al, 1994). A further study casts doubt on this data and has shown similar rates of antibodies to bovine serum albumin among patients with type1 diabetes, healthy controls and those with other autoimmune disorders (Atkinson et al, 1993).

A number of ecological studies have been performed which examine national cow's milk consumption and the incidence of type 1 diabetes (Fava et al, 1994; Muntoni et al, 1994; Scott, 1990; and Dahl-Jorgensen et al, 1991). These studies suggest a strong correlation (r=0.96) between the incidence of type 1 diabetes and the annual national cow's milk consumption (Scott, 1990 and Dahl-Jorgensen et al, 1991). Fava et al (1994), also describe an association between the incidence of diabetes and cow's milk consumption but show that while Finland and Sardinia have a similar incidence of diabetes, Finland has more than twice the annual consumption of cow's milk. It should also be noted that these are population studies and do not confirm that those individuals with higher milk consumption are those with diabetes.

Epidemiological studies from Norway and Sweden have shown that the incidence of diabetes increases with decreased duration of breast feeding and that

the time lag between the two factors is approximately 10 years (Borch-Johnson et al, 1984). However, no change in incidence was noted in the United States with reduction in the rates of breast-feeding.

A meta-analysis performed by Gerstein (1994), found that in case-control studies patients with type 1 diabetes were more likely to have been breast fed for less than 3 months (OR = 1.43) and to have been exposed to cow's milk before the age of 4 months (OR = 1.63). Verge et al (1994) similarly note a protective effect of prolonged breast-feeding. Gerstein concludes, that "early cow's milk exposure may be an important determinant of subsequent type 1 diabetes and may increase the risk ~1.5 times". There has been criticism of the methodology employed in some of these case-control studies particularly in the reliance of parental recall of the early infant diet. Patterson et al (1994), in their study in Northern Ireland and Scotland failed to demonstrate a protective effect of breast feeding.

There is much conflicting evidence regarding the role of cow's milk and breast-feeding in the aeitiology of type1 diabetes. A large prospective randomised control study of early infant feeding is currently underway in Finland, it is hoped that this study will answer many of the questions raised to date.

1.9 Family History of Diabetes

While there is documented genetic susceptibility to the development of diabetes up to 80% of those with the disease will not have a positive family history

(Bennett, 1985). The proportion of those with insulin-dependent diabetes in a first degree relative has been variably reported as 8.9%(Metcalfe and Baum, 1992), 11% (Bloom et al, 1975), 12.8% (Dahlquist et al, 1985), and 23% (Calnan and Peckham, 1977). In a study of diabetes in those aged under 5years a positive family history was noted in 16% of those diagnosed under 5yrs compared with 10% diagnosed between age 5 and 10 years (Jefferson et al, 1985).

In a Swedish study of over 2,000 children with diabetes 8.1% had a parent with insulin dependent diabetes. In twice as many cases this parent was the father (5.7% vs 2.4%) (Dahlquist et al, 1985). Metcalfe and Baum (1992) in the U.K., similarly report almost double the frequency of insulin dependent diabetes in fathers at 3.5% with mothers at 1.9%. Previous studies have shown the risk of a child developing IDDM if the father is affected is 4-6% while this is halved if the mother is the affected parent, the risk being 2-3%(Jefferson et al, 1985).

No association was found between the age of disease onset and presence of a positive family history in Swedish children (Dahlquist et al, 1985). However, in British children an earlier onset of diabetes was noted in those with an affected father but not an affected mother. The age of diagnosis of the child and father were found to be associated. The age at diagnosis of a child and an affected sibling were also associated but only if the sibling was of the same sex (Metcalfe and Baum, 1992).

1.10 Birth Order

A number of studies have demonstrated an increased risk of diabetes in first born children (Wager et al, 1983 and Ramachandran et al, 1993). Patterson et al (1994), found the increased risk to the first born only in Northern Ireland and not Scotland in their case control study, Odds Ratio 1.41 (95% CI 1.03-1.93). Other studies have failed to demonstrate an increased risk in first born children (Bock et al, 1994 and McKinney et al, 1999). Dahlquist et al (1999) in their study report a protective effect against diabetes in the first born but do not provide any information about the magnitude of this effect.

The increased risk to the first born is postulated to relate to effective isolation of children in early infancy from infectious contacts in the absence of a sibling. This relates to the hygiene hypothesis discussed earlier. The impact, if any, of birth order on the risk of diabetes development remains unresolved.

1.11 Household Occupants

The number of occupants in the home has been considered as a potential risk factor in the development of diabetes, however, the data in this regard is conflicting. Patterson et al (1994), found that homes with 6 or more occupants showed a slight but not significant reduction in diabetes. Other studies have

shown an increased risk of diabetes when living in larger groups (Siemiatycki et al, 1989 and Lawler-Heavner et al, 1991).

Blom et al (1989), showed no difference in the number of siblings between cases and controls in Sweden. The number of siblings is likely to be highly associated with the number of persons living in a single house.

1.12 Presenting Clinical History

Diabetes in children and adolescence has an abrupt clinical onset in two to three weeks in most cases. However, the duration of symptoms prior to diagnosis can vary from a few days to several months (Becker and Weber, 1995). The duration of symptoms tends to be shorter in younger children, this was found by Jefferson et al (1985), in their study where 30% of children under 5 had a history of symptoms of less than 2 weeks compared to 12% of those aged 5-10years.

It is estimated that 90% of β-cells pancreatic function is lost prior to the onset of clinical symptoms. In this group diabetes is characterised by insulin deficiency and hyperglycaemia. Children are prone to the development of ketoacidosis which tends to develop where there is a longer duration of severe insulin deficiency. Left untreated with insulin diabetes is rapidly fatal in children.

Clinical symptoms include polyuria, polydipsia, polyphagia, weight loss, lethargy, blurring of vision, eneuresis in a previously toilet trained child, and infections. Symptoms develop due to underlying hyperglycaemia, energy

wasting and alteration in immune function. These children may present to medical attention in the acute life-threatening condition of diabetic ketoacidosis which is characterised by dehydration, hyperglycaemia, nausea, vomiting, abdominal pain, acidosis, alteration in consciousness, ketonuria and glycosuria. Polyuria, polydipsia and weight loss are the commonest symptoms noted in 73% of those under 5 years and 81% aged 5-10 by Jefferson et al (1985).

The reported frequency of presentation in diabetic ketoacidosis (DKA) is variable. Komulainen et al (1999), found younger children presented more often in diabetic ketoacidosis. In their study 53.3% of those aged less than 2 years presented in diabetic ketoacidosis. In 10% of those under 2 years the ketoacidosis was considered severe, defined as pH <7.10, compared with 2.9% in the group aged 2-4.9 and 4.7% of those aged 5-14.9 years. In the Oxford region, Pinkney et al (1994), studied a cohort of 230 patients with insulin-dependent diabetes diagnosed before age 21years in 1985 and 1986. They found that 16% were in severe diabetic ketoacidosis at presentation, with pH <7.10 or plasma bicarbonate < 10mmol/l, and 10% had mild to moderate diabetic ketoacidosis at presentation, with pH 7.10- 7.35 or plasma bicarbonate 10-21mmol/l. A further 97 patients studied in 1990 found similar occurrence of severe ketoacidosis (13%) and mild to moderate ketoacidosis (13%). Presentation in severe ketoacidosis was more common in younger children less than 5 years. Ketoacidosis at presentation was found to be less common with increasing age.

1.13 Summary of Introduction and Literature Review

Diabetes Mellitus is an important chronic medical condition causing significant morbidity, disability and premature mortality. Type 1 or insulin-dependent diabetes, accounts for the vast majority of diabetes in children and young adults. This disease has an abrupt onset and in the absence of prompt diagnosis and treatment with insulin, is rapidly fatal.

Diabetes has been described for centuries yet its aeitiology remains unknown. Epidemiological studies have been of great benefit in identifying the magnitude of the burden of diabetes worldwide, monitoring changes in the patterns of diabetes and casting some light on potential aeitiologies. The pathophysiological process in diabetes development is the autoimmune destruction of the insulin producing β cells of the pancreas. A number of autoantibodies have been identified, such as: islet cell antibodies (ICAs); insulin autoantibodies (IAAs); autoantibodies to glutamic acid decarboxylase (GAD_{65}); and autoantibodies to tyrosine phosphatases IA-2 and IA-2β. These antibodies are markers of destruction of the insulin producing β-cells. What initiates this process of autoimmune pancreatic destruction is unknown.

There is a genetic component in the development of diabetes, which is complex and polygenic. To date more than 15 different loci are thought to be involved in protection from or susceptibility to the development of diabetes. Currently the strongest association has been linked to the HLA region on chromosome 6 and certain HLA B, DR and DQ alleles. However, genetic susceptibility is not the

only factor important in disease development as is shown by the high rate of disease discordance among genetically identical monozygotic twins. In fact up to two-thirds of people with the genetic predisposition to diabetes will never develop the disease. Similarly while individual studies vary regarding actual percentages, they all demonstrate that the majority of children who develop diabetes do not have a positive family history of the disease.

The current thinking is that one or possibly a number of environmental agents act on the genetically predisposed to trigger the development of diabetes. Environmental agents proposed as causative agents, include: infectious diseases; environmental toxins; dietary factors and stress.

Epidemiological studies provide strong support for the role of environmental agents in disease development. There is wide international variation in the incidence of diabetes. The highest incidence of the disease is in Europe and the lowest in Asia. The country with the highest incidence in the world is Finland at 42.9 per 100,000per year and the lowest is China at 0.5 per 100,000 per year. It is a disease of more temperate climes that generally increases in frequency with northern travel from the equator. It does not, however, follow a strict north-south gradient. Sardinia for example has the second highest incidence in Europe despite its southern position. Geographical and ethnic variation in disease incidence could be explained on the basis of differing genetic compositions in each population. Certainly the disease is most common in Caucasians than those of Asian or African origin. However, there are documented variations in disease incidence within countries whose populations have the same ethnic and probably,

genetic background. Migrant studies of those who migrate from low to high incidence countries over time have an incidence rate of diabetes that approaches that of their adoptive country. This data would support a strong environmental influence. Criticisms of these migrant studies in proving an environmental effect lie in their failure to demonstrate a reduced incidence of disease on migration from an area of high to low incidence. The pattern of migration in large volumes tends to be from East to West, from Africa and Asia to Europe and North America. Thus, migration in large numbers tends to be from areas of low disease incidence to areas of high incidence. One area where there has been significant migration from an area of high incidence to one of low incidence is in Italy, with migration from Sardinia to nearby Lazio. Children of Sardinian heritage retain a higher incidence of disease similar to that in Sardinia if both parents are from Sardinia and almost half the Sardinian incidence if only one parent is from Sardinia, both rates are significantly higher than that of Lazio heritage children. The experience of Sardinian heritage children born in nearby low incidence Lazio show a pattern of risk that is more suggestive of a strong genetic rather than environmental effect. However, all other migrant studies do suggest a strong environmental effect.

The rising incidence of diabetes that has been documented in many countries world-wide and most countries of Europe, supports an environmental effect. The rate of increase in the disease is too rapid to be explained by changes in population genetics alone.

The incidence of diabetes in the British Isles is high in keeping with its northern latitude. However, little data is available for diabetes incidence in Ireland. Two previous studies that included Ireland both showed a significantly lower incidence of disease in Ireland than other areas of the British Isles. In neither study was a measure of case ascertainment provided for Irish data and so there was concern that the low incidence rate reported was due to underreporting of cases. An increasing incidence of diabetes has been demonstrated in other areas of the British Isles. No such data is available for Ireland. Accurate information regarding the incidence of chronic disease, particularly one which has its onset in childhood, is important for strategic planning at both policy and service provision levels.

Type 1 (insulin-dependent) diabetes has an abrupt clinical onset over a period of weeks to months. The typical symptoms are of polyuria, polydipsia, weight loss and lethargy. A variable number of those with diabetes present with an acute life-threatening state of metabolic decompensation termed diabetic ketoacidosis.

The age of onset of diabetes has been shown to have a bimodal distribution, in the majority of studies. The incidence rises throughout childhood with a peak in early adolescence, which is earlier in females than males, and a smaller peak in the early childhood years. It is postulated that the earlier peak incidence in females is related to the earlier onset of their pubertal growth spurt.

The incidence of diabetes is slightly higher in males in countries of high incidence. Low incidence countries tend to have a slight female predominance.

Seasonality has been described in diabetes as in many other conditions shown to have an infectious aetiology. The highest number of new cases being diagnosed in Autumn/Winter and the lowest number in the warmer Summer months. Several studies have noted the absence of a seasonal trend in those diagnosed under the age of 5 years. However, this may be due to small numbers in this age group when considering centres individually. The EURODIAB ACE study of 26 centres confirmed seasonality for both sexes and in all age groups.

Dietary factors are considered potentially important aetiological factors. Much attention is now directed towards the early introduction of cow's milk as a potential initiating environmental factor in disease development. A number of studies have shown a protective effect of breast-feeding. Many countries document an increase in the incidence of diabetes with falling rates and duration of breast-feeding, although this has not been the case in the United States. Prospective case control studies of infant feeding are now in progress to evaluate the aetiological role of cow's milk protein in diabetes.

The aim of these epidemiological studies is to increase understanding of diabetes through study of the patterns of disease occurrence. In this way hypotheses regarding aetiology may be generated and tested, leading ultimately to the identification of the aetiology of type 1 (insulin-dependent) diabetes. When the aetiology of diabetes is understood it may then be possible to prevent the development of the disease in those who are genetically predisposed.

1.14 Aims – Purpose of the Study

The aim of this study was to identify characteristics of insulin-dependent diabetes in an Irish cohort of patients, namely to:

1. Establish a national incidence rate of insulin-dependent diabetes in children and adolescents aged less than 15 years in the Irish Republic (hereafter referred to as "Ireland")
2. Determine the age of onset of diabetes
3. Determine the sex profile
4. Determine the season of onset
5. Identify the method of infant feeding
6. Identify the frequency of a family history of Diabetes
7. Determine the birth order
8. Determine the family size
9. Identify the presenting clinical history

Seek clustering of cases by season of diagnosis and by month and year of birth.

CHAPTER TWO

METHODS

2. METHODS

2.1 Case Definition

The case definition of diabetes employed in this study, required that cases were:

1. diagnosed by a physician as having diabetes mellitus
2. commenced on daily insulin prior to their 15th birthday and
3. resident in Ireland at the time of diagnosis

This case definition is similar to that used in the World Health Organisation Multinational Diabetes Mondiale – Diamond Study (1991). Cases were excluded if diabetes was secondary to another condition such as cystic fibrosis.

2.2 Ethical Approval

Ethical permission for the study was granted by the joint ethics committee of the Federated Dublin Voluntary Hospitals. A condition of ethical approval was that patient names should not be entered on a computer.

2.3 Incidence of Diabetes

Incidence is an appropriate measure of disease frequency to use in the study of diabetes in childhood and adolescence because of the characteristics of the disease in this age group. Disease incidence measures the number of new or

"incident" cases of disease occurring in a population at risk in a specified time period.

The study of disease incidence requires that a disease be readily identifiable. Diabetes in childhood and adolescence has a distinct and rapid onset, and in the absence of insulin administration these patients will die. It is therefore a condition well suited to the study of incidence as those with the disease promptly come to medical attention. In diabetes there is a prolonged phase of pre-clinical disease, the phase of pancreatic destruction, but the time from clinical disease onset to diagnosis is short.

2.4 Identification of Incident Cases - Data Collection

In identifying cases, the aim was to include as close to all new, or incident cases, of diabetes in the population under 15 years in a single year. It is the practice in Ireland that children with insulin dependent diabetes are admitted to hospital at the time of diagnosis for stabilisation and education; as a result a hospital-based study could be expected to identify the majority of new cases. International data would suggest that the majority of insulin-dependent diabetes occurring in childhood and adolescence presents under the age of 16 years. Children under the age of 14 years present to paediatricians and increasingly Irish paediatricians tend to care for children up to the ages of 16 or 17 years. Identification of new cases of diabetes in this age group in Ireland by hospital based paediatricians

should identify the majority of cases and would form the main source of case identification.

Following review of the international literature and discussion with experts in Ireland and abroad, including Professor Jaakko Tuomilehto, European co-ordinator of the World Health Organisation DiaMond project, the questionnaire used in this study was developed by the investigator. It was decided that a prospective study be performed to avoid the problems of recall associated with retrospective studies. The questionnaire sought patient information such as the patient's name, date of birth and date of diagnosis. It sought family information such as the number of occupants in the family home, the number of siblings and birth order. Questions were asked relating to the child's feeding history in infancy and the presence or absence of any significant medical condition. Additional questions were asked relating to the diagnosis of diabetes mellitus namely the duration of symptoms and presenting symptoms. The presence of a family history of diabetes was also sought. The questionnaire used is displayed in Appendix II.

Following discussions with and the submission of a study protocol to the Irish Paediatric Surveillance Unit (IPSU) they agreed to support this project. The initial case identification was performed through the mechanism of the IPSU.

The Irish Paediatric Surveillance Unit is modelled on the highly successful British Paediatric Surveillance Unit (BPSU). The BPSU, which was established in 1986, has been an invaluable mechanism for the study of uncommon

conditions in childhood in the British Isles (Hall and Glickman, 1988). Participating paediatricians in the BPSU include those from the United Kingdom and Ireland. Professor David Baum and Alison Metcalfe, through the BPSU performed a previous very successful study of the incidence of diabetes in children in the British Isles. The current study follows a similar methodology in initial case identification.

The IPSU was established in 1997, by Professor Dennis Gill and Dr Anita Menon, its purpose is to collect data from paediatricians relating to designated conditions of interest. All paediatricians in Ireland are notified in advance of three to four conditions that will be investigated in each year by the Irish Paediatric Surveillance Unit. Paediatricians are then sent a monthly card where they are required to notify if they have seen a case of the condition under study, which meets the previously circulated study criteria. The monthly reporting card also includes an option of "nothing to report", which is returned when the reporting paediatrician has not seen any cases of the condition under study in that particular month. The reports from paediatricians are then sent to the investigator of each condition. Insulin dependent diabetes was included as a condition for study in 1997.

The study criteria requested paediatricians to notify all new cases of diabetes requiring insulin therapy, presenting for the first time under the age of 18 years, between January 1st, 1997 and December 31st, 1997. The age of 18 years was chosen to ensure maximum case ascertainment in the 0 to 15 year age group under investigation.

All paediatricians who notified new cases of diabetes were asked to confirm the total number of new cases of diabetes that they had seen and were sent a questionnaire to complete on each patient. This questionnaire sought to confirm the initial case report and also to obtain additional patient information, as described above. Only cases that were confirmed on follow-up questionnaire to fulfil the study criteria were included in the analysis. Cases that were initially notified but not confirmed with additional data were excluded from the analysis. Strenuous efforts were made to confirm all reported cases by letter and telephone. To include cases without additional confirmatory information could result in double counting of cases, as it would not be unusual for children with diabetes to attend more than one centre.

Those paediatricians participating in the Irish paediatric surveillance unit who did not notify any new cases of diabetes in the time period were contacted to ensure that no new cases had been seen.

In addition to contacting paediatricians, diabetes nurse specialists were also contacted to ensure that no cases had been missed.

There are geographical areas, and hospitals in Ireland who do not currently, have access to paediatric services and patients in these areas will either be transferred to other units with paediatric services or will be cared for by at adult physicians. It is also possible that children under the age of 15 with diabetes could present to adult physicians or adult endocrinologists rather than paediatricians. While the majority of new cases of diabetes in this age group, it is believed, would present

to paediatric services it was felt that to rely on securing data from paediatric centres alone would result in an under estimation of the incidence of the condition.

The Irish Endocrine Society, which represents the consultant endocrinologists, both adult and paediatric, in the country agreed to support and inform its members of this study. All endocrinologists in the country were contacted and asked to notify new cases of diabetes seen in the time period. All institutions in the State that care for those with diabetes do not have an endocrinologist on staff, and so all hospitals and all physicians in the country were contacted to ascertain if new cases of diabetes had presented to them between the 1st January and December 31st, 1997.

2.5 Secondary source of case ascertainment

The methodology outlined above aimed to maximise case identification by exploring all possible avenues of patient presentation to hospital. However, the accuracy of any incidence rates generated from this data would depend on the degree of completeness of case identification. While it is believed that this methodology should capture the vast majority of new cases of diabetes in the population in this time period, the potential remains that incident cases could be missed. In order to estimate the degree of ascertainment of the hospital based case identification, a secondary ascertainment source was sought. This secondary source of data was independent from that of the initial data collection. This is to ensure that new cases of diabetes have an equal probability of being in

the secondary data source whether or not they were in the primary data source. A number of potential secondary sources of case ascertainment were considered, such as: centralised hospital discharge data; diabetes patient associations; insulin prescriptions; and centralised governmental health care support schemes for those with diabetes.

The centralised government healthcare support schemes for those with diabetes was chosen as the most appropriate secondary source of case ascertainment. The particular advantages of this data source are that its remit is nationwide and its records are computerised. The Irish health care system provides insulin free of charge to all those in the State who require it, independent of their means. Patients may avail of free insulin therapy in two ways, they may have a long-term illness card (LTI) or a General Medical Services card (medical card). The General Medical Services scheme or long-term illness scheme are both administered by the General Medical Services (Payments) Board. Following discussion with the General Medical Services (Payments) Board they agreed to give information from their records of the number of patients that had received a long-term illness card or GMS card for diabetes mellitus issued for the first time in the study period, 1997. Due to ethical considerations of patient confidentiality the Board did not feel it appropriate that I directly access their records but did agree to cross-check the study data with their records.

Using this government based computerised data as an independent method of new case identification, the capture-recapture method could be applied to estimate the true number of incident cases of diabetes in the population. The

capture-recapture method requires the use of two independent data sources. This is a method widely used for estimation of population size in a closed population (Cochi et al, 1989; LaPorte, 1994; International Working Group for Disease Monitoring and Forecasting, 1995; LaPorte et al, 1993). It is a methodology well established in the study of diabetes incidence.

2.6 Population Data

Population data was derived from the 1996 census of population provided by the Central statistics Office (1997). Intercensal estimates of population for 1997 were also provided by the Central Statistics Office (1999). The intercensal estimates were used in calculations. Population data is displayed in Appendix IV.

2.7 Data Analysis

The data was analysed using a personal computer, DELL Pentium computer and software program SPSS version 8.

2.7.1 Calculation of Incidence Rates

Disease incidence is defined as the number of new cases of disease presenting in a population at risk in a given time period. An incidence rate, or incidence density, is calculated by the formula:

Incidence Rate = number of new cases of disease in a given time
/Density total person-time of observation (ie at risk)

(Hennekens and Buring, 1987)

In presenting an incidence rate the time period of study must be stated.

Incidence rates presented for an entire population are summary rates, termed Crude Rates.

Category-specific incidence rates are presented for categories of the population defined by a characteristic such as age, sex or race. Thus, a category specific incidence rate of disease would be calculated from the number of new cases of disease occurring in a particular age group divided by the total number in that stratum at risk of the disease, in a specified time period.

2.7.2 Calculation of Confidence Intervals for Incidence Rates

95% confidence intervals based on the Poisson distribution were derived for incidence data using the software program STATA. Where:

"given a count k, the expected is k and the standard deviation $\sqrt{k}$. ci calculates the exact confidence interval $[k_1, k_2]$ such that $\Pr(K \leq k_1) \leq \alpha/2$ and $\Pr(K \geq k_2) \leq \alpha/2$. Solution is by Newton's method. If $k = 0$, the calculation of k_1 is skipped. All values are reported as rates, which are the above numbers divided by total exposure" (STATA Corp., 1997).

2.7.3 Standardisation of Incidence Rates

It is not valid to compare crude incidence rates between populations, as there are differences in the composition of each population, particularly differences in age and sex. Failure to take account of underlying differences in population structure would lead to erroneous conclusions of disease frequency. As a result incidence rates must be adjusted or standardised, to compensate for differences in age and sex between the populations and allow comparison. The resulting standardised rate is an artificial mathematically constructed figure. Standardisation of incidence rates was performed using the direct method of standardisation where the category–specific rates, defined above, were applied to the common standard population which assumes equal numbers in each of the age groups 0-4.9, 5-9.9, and 10-14.9 years for each sex. The directly standardised rate can be defined by:

$$R_{(adj)} = \frac{\Sigma N_i r_i}{\Sigma N_i}$$

Where i represents the age group, r_i is the age-specific rate in the study population and N_i is the standard population in age group i (Daly et al, 1991, pg 278).

2.7.4 Calculation of Confidence Intervals for standardised rates

95% confidence intervals were calculated for directly standardised incidence rates using the following formula:

$$R_{(adj)} \pm 1.96 \text{ SE } (R_{(adj)})$$

Where: $$SE\ (R_{(adj)}) = \frac{\sqrt{\Sigma N_i^2 r_i/n_i}}{\Sigma N_i}$$

Where n_i is the number in the study population on which the age-specific rate (r_i) is based (Daly et al, 1991, pg 279).

2.7.5 Estimates of the Probability of Ascertainment

The determination of completeness of ascertainment and estimation of the true number of incident cases in the population was made using the capture-recapture method. The estimate of the total number of incident cases of IDDM was made using the following formula (LaPorte et al, 1993):

$$N = \frac{(M+1)\,(n+1)}{(m+1)} \quad -1$$

Where N is the total number of incident cases of diabetes, M is the number of cases identified in the primary source (the capture), n is the size of the secondary source (the recapture) and m is the number of cases included in both sources.

The variance of N is estimated by:

$$Var(N) = \frac{(M+1)\,(n+1)\,(M-m)\,(n-m)}{(m+1)^2(m+2)}$$

The 95% confidence interval for the estimate of the total number of cases is:

$$95\%\ C.I. = \pm 1.96\sqrt{Var\ (N)}$$

The degree of completeness of case ascertainment for each source is identified using the following equations (WHO Multinational Project for Childhood Diabetes, Diabetes Mondiale – DIAMOND, 1991):

Primary Source, percentage ascertainment $= M \div N * 100$

Secondary Source, percentage ascertainment $= n \div N * 100$

Total estimated ascertainment $= \frac{[M + (n-m)]}{N} * 100$

2.7.6 Statistical Analysis

Following consultation with the Department of Statistics, Trinity College further analysis was performed using the statistical techniques of the Chi square test and probability testing, as calculated from the following equation:

$$X^2 = \frac{\sum (\text{Observed} - \text{Expected})^2}{\text{Expected}}$$

The exact Chi square test being used where necessary, that is, where more than 20% of cells have expected counts less than 5. The student's t-test and the Kursten Wallis test was used where appropriate to compare groups. Log linear modelling was also used.

Edward's (Edward, 1961) and Roger's (Roger, 1977) tests were applied to assess seasonality following discussion and with the assistance of Dr. Chris Patterson, Department of Epidemiology and Public Health, Queen's University of Belfast and the Royal Victoria Hospital.

CHAPTER THREE

RESULTS

3. RESULTS

3.1 Incident Cases

The number of new cases of diabetes meeting the diagnostic criteria identified in the study period was 140. A total of 103 cases were notified to the Irish Paediatric Surveillance Unit (IPSU), of these 10 were repeat notifications. The IPSU response rates are outlined in Appendix III. One report could not be confirmed and was excluded from the analysis. In 2 cases diabetes was related to cystic fibrosis and these cases were also excluded from the analysis.

A further 37 cases were identified on follow-up questionnaire, these were due to initial under-reporting of cases by Paediatricians participating in the IPSU and by contacting Paediatricians who had not returned notifications to the IPSU. A further 11 cases were identified from adult physicians, endocrinologists and diabetes nurse specialists.

The overall response rate from paediatricians was 98.6% and 71% from adult physicians.

3.2 Age Category at Diagnosis

The incident cases were divided into three age categories (see Table 3.1). 27 cases (19.3%) were in the age range 0 – 4.99 years at diagnosis; 59 (42.1%) were aged between 5 and 9.99 years; and 54 (38.6%) were in the age category 10 –

14.99 years. There was a significant difference in the age category at diagnosis, with a lower number of cases than expected diagnosed in the 0 – 4.99 year age category (χ^2 12.7; df 2; p = 0.002).

Table 3.1 ***Age Category at Diagnosis***

Age Category	Number of Cases	Percentage
0 - 4.99 years	27	19.3%
5 – 9.99 years	59	42.1%
10 – 14.99 years	54	38.6%
Total under 15 years	140	100.0%

3.3 Sex

Overall 73 (52.1%) cases were male and 67 (47.9%) female. The male to female ratio of cases was 1.09:1. The ratio of males to females in the general population under the age of 15 years was 1.06:1. There was a slight excess of male cases but this did not reach statistical significance.

In the three age categories 0-4.99, 5 – 9.99 and 10 – 14.99 years: 12 (44.4%) cases were male and 15 (55.6%) female; 29 (49%) were male and 30 (50.8%) female; and 32 (59.25%) were male and 22 (40.7%) female, respectively.

Table 3.2 *Sex by Age Category*

Age Category	Sex		Total
	Male	Female	
0 – 4.99 years	12	15	27
5 – 9.99 years	29	30	59
10 – 14.99 years	32	22	54
	73	67	140

3.4 Incidence Rates

The overall crude incidence rate of diabetes in those aged under 15 years, in 1997, was calculated at 16.6 per 100,000 per year (95% confidence interval 13.9 – 19.5).

The overall incidence rate for males aged less than 15 years was 16.8 per 100,000 per year (95% confidence interval 13.2 – 21.1).

The overall incidence rate for females aged less than 15 years was 16.3 per 100,000 per year (95% confidence interval 12.6 – 20.7).

3.4.1 Category Specific Incidence Rates

Age-specific rates

The age-specific incidence rate for those aged 0-4.99 years, was calculated at 10.8 per 100,000 per year (95% confidence interval 7.1 – 15.7).

The age-specific incidence rate for those aged 5 – 9.99 years, was 21.3 per 100,000 per year (95% confidence interval 16.2 – 27.4).

The age-specific incidence rate for those aged 10 – 14.99 years was 17.0 per 100,000 per year (95% confidence interval 12.8 – 22.2).

Age and Sex- specific incidence rates

The incidence rate for males aged 0-4.99 years, was calculated at 9.3 per 100,000 per year (95% confidence interval 4.8 – 16.3). The incidence rate for females aged 0-4.99 years, was calculated at 12.4 per 100,000 per year (95% confidence interval 6.9 – 20.4).

The incidence rate for males aged 5 - 9.99 years was calculated at 20.4 per 100,000 per year (95% confidence interval 13.7 – 29.3). The incidence rate for females, aged 5 - 9.99 years, was calculated at 22.1 per 100,000 per year (95% confidence interval 14.9 – 31.6).

The incidence rate for males aged 10 - 14.99 years was calculated at 19.6 per 100,000 per year (95% confidence interval 13.4 – 27.7). The incidence rate for females aged 10 - 14.99 years was calculated at 14.2 per 100,000 per year (95% confidence interval 8.9 – 21.6).

Table 3.3 Crude *and Category Specific Incidence Rates*

Age Category	Male Rate* (95% CL)	Female Rate* (95% CL)	Total male and female Rate* (95% CL)
0 – 4.99 years	9.3 (4.8, 16.3)	12.4 (6.9, 20.4)	10.8 (7.1, 15.7)
5 – 9.99 years	20.4 (13.7, 29.3)	22.1 (14.9, 31.6)	21.3 (16.2, 27.4)
10 – 14.99 years	19.6 (13.4, 27.7)	14.2 (8.9, 21.6)	17.0 (12.8, 22.2)
Total 0 – 14.99 years	16.8 (13.2, 21.1)	16.3 (12.6, 20.7)	**16.6 (13.9, 19.5)**

* number of cases per 100,000 per year, **CL** = confidence limits

3.4.2 Standardised Incidence Rates

Standardised incidence rates were calculated using the direct method of standardisation, applying the above category-specific rates to the common standard population, which assumes equal numbers in the three age categories for each sex. The standardised incidence rate for those aged less than 15 years was 16.3 per 100,000 (95% confidence interval 14.2 – 18.5). The standardised rate for males under 15 years was 16.4 per 100,000 per year (95% confidence interval is 13.5 – 19.4) and for females under 15 years was 16.2 per 100,000 per year (95% confidence interval is 13.2 – 19.3).

3.5 Estimate of Ascertainment

The secondary source of case ascertainment yielded 153 cases. Of these cases 101 cases were common to both the primary and secondary source. Using the capture-recapture formula shown in Chapter 2, the estimate of the total number

of cases of diabetes is 211.9(N). The variance of N is 41.1 and 95% confidence interval of 199.3- 224.4.

The estimated ascertainment is thus: 66% for the primary source; 72.2% for the secondary source; and 90.6% for both sources combined. However, there is concern regarding the accuracy of the data in the second source. The particular concern relates to the reliability of coding for diabetes in the second source. If non-diabetic cases are included in the numbers reported from the secondary source an overestimate of the total number with diabetes results (see Chapter 4, section 4.6).

3.6 Age of Onset

The overall mean age of onset was 8.7 years, standard deviation 3.7 years, and range of 13.8 years, from 1.09 to 14.89 years. Figure 3.1, below shows the age of onset in years, the data has been rounded for presentation.

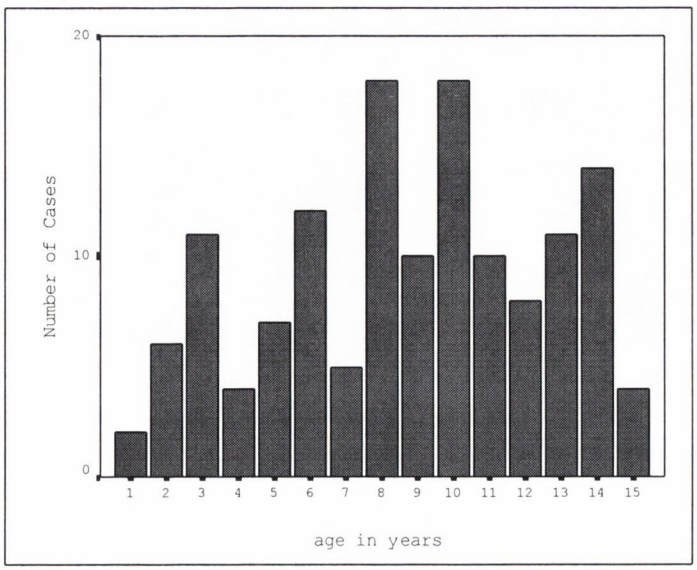

Figure 3.1 Age at diagnosis in years - males and females

The mean age of onset for females was 8.2 years, standard deviation 3.6 years and range of 1.09 to 14.81 years. The number of cases diagnosed in girls generally rose through childhood to a small peak at 5 years, then declined and reached a maximum peak at 8 years and then declined with a second smaller peak at 14 years (see figure 3.2).

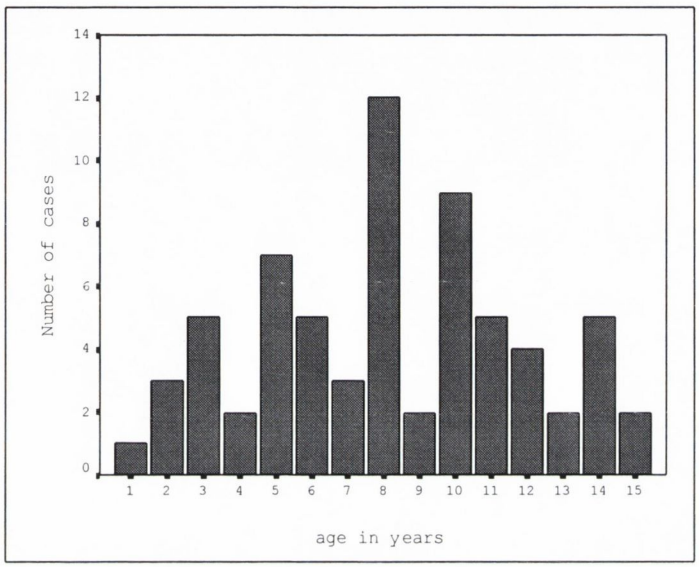

Figure 3.2 ***Age of Onset of Diabetes – Females only***

The mean age of onset for males was 9.2 years, standard deviation 3.8 years, and range of 1.28 to 14.89 years. In boys the peak onset was at ages 9, 10, 13 and 14 years, with smaller peaks at ages 3 and 6 years (see figure 3.3 below).

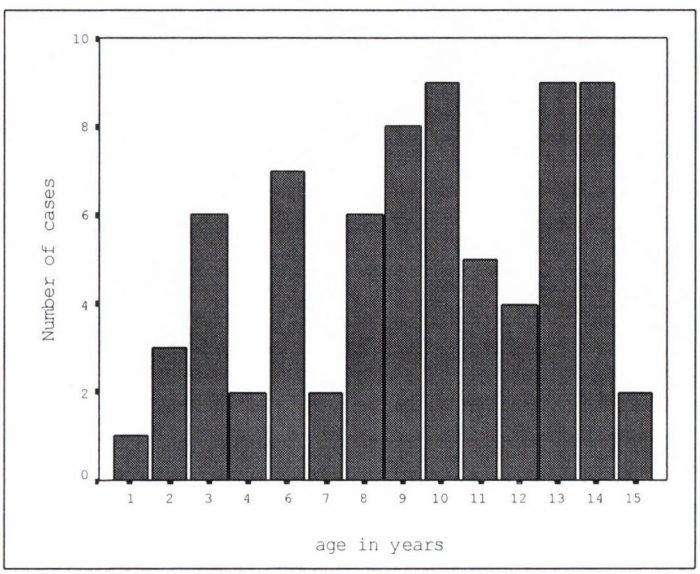

Figure 3.3 ***Age of Onset of Diabetes – Males only***

There was no significant difference in the age of diagnosis of diabetes in boys or girls (t-test 1.6; df 138; p=0.106).

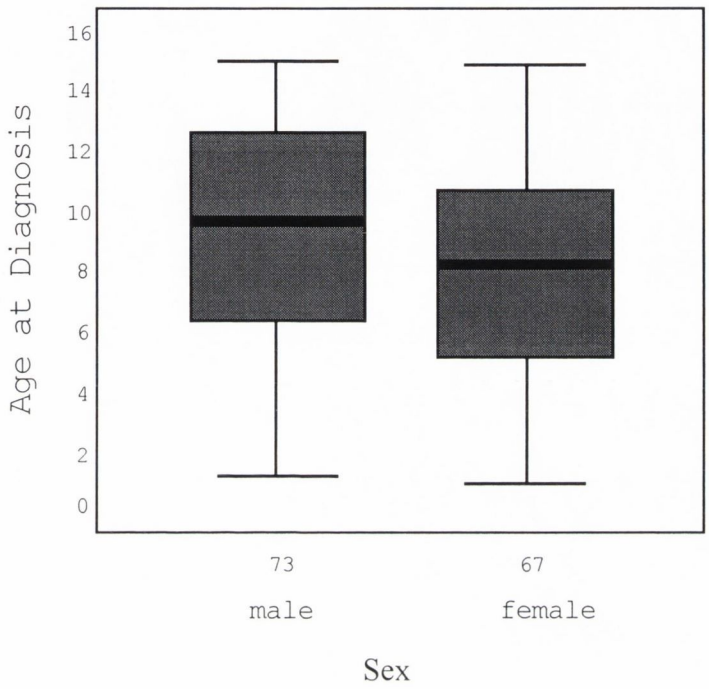

Figure 3.4 Boxplot of Age at Diagnosis by Sex

3.7 Age clustering

Frequency of Cases by Year of Birth

Of the new cases of diabetes diagnosed in 1997, 19 cases or 13.6% were born in 1987 and 12.9% were born in 1989. In other years the range was from 1.4 to 9.3% of cases (see Figure 3.4). The number of cases was too small to demonstrate significant clustering by year of birth.

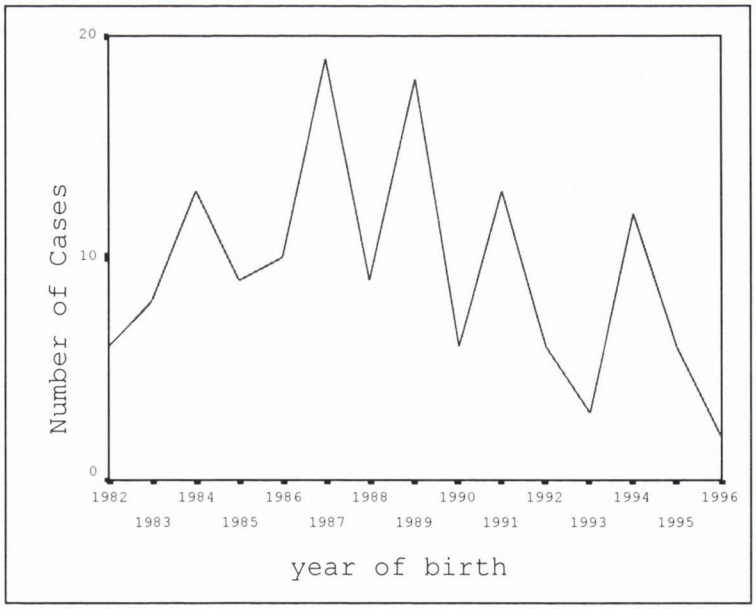

Figure 3.5 Cases of Diabetes by Year of Birth

Frequency of Cases by Month of Birth

The most frequent months of birth were July (14.3%), December (12.1%), June (11.4%) and October (10%). The least frequent month of birth was November (4.3%). There was no significant difference when analysed by month of birth (χ^2= 18.2; df 11; p = 0.076).

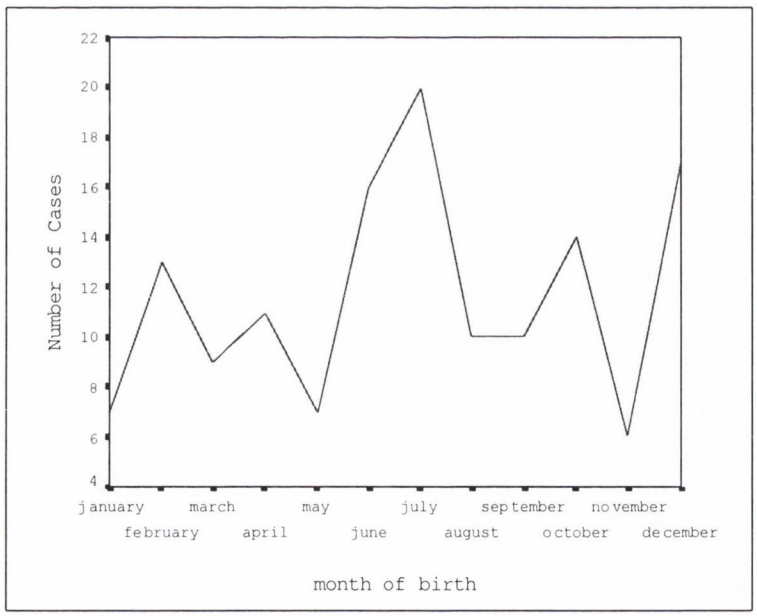

Figure 3.6 Frequency of cases by month of birth

When analysed by month and year of birth the number of cases was too small to demonstrate clustering of cases.

3.8 Season of Onset of Diabetes

The majority of cases were diagnosed in autumn (45 cases or 32.1%). There were 35 cases (25%) in Winter, 32 cases (22.9%) in Summer and 28 cases (20%) diagnosed in Spring.

Table 3.4 Season of Onset of Diabetes

Season	Number of Cases	Percentage
Spring	28	20%
Summer	32	22.9%
Autumn	45	32.1%
Winter	35	25%
Total	140	100%

Figure 3.7 shows the season of onset of diabetes in the total study population.

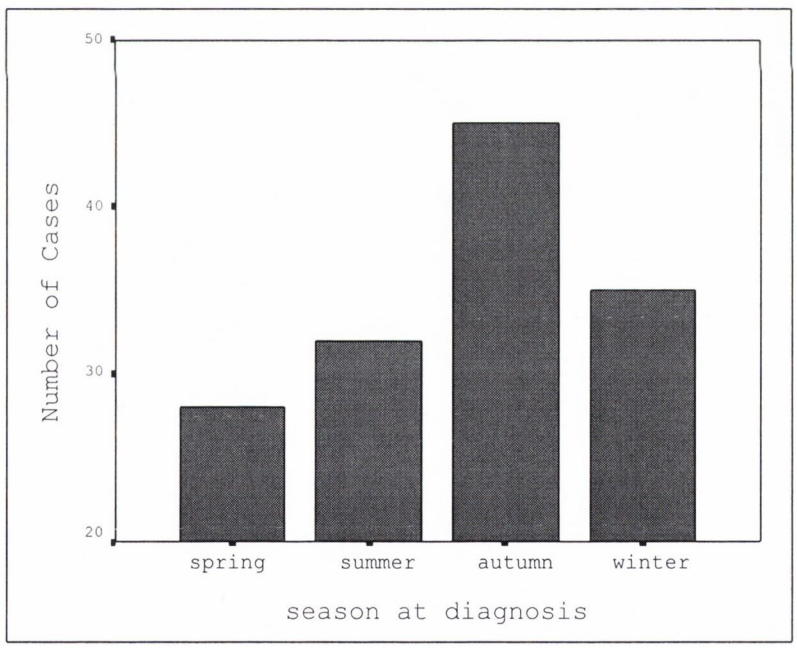

Figure 3.7 Season at Diagnosis of Diabetes

When analysed by sex, 45.2% of male cases (33) were diagnosed in Autumn and 24.6% (18) in Winter. The lowest number of cases for males were diagnosed in

Summer and Spring, at 13.7% (10) and 16.4% (12) respectively. In females, the highest number of cases were diagnosed in Summer at 32.8% (22). The remaining cases were diagnosed in Winter (17), Spring (16) and Autumn (12) accounting for 25.4%, 23.9% and 17.9% respectively.

Table 3.5 Season of Onset of Diabetes by Sex

Sex	Spring	Summer	Autumn	Winter	Total
Male	12	10	33	18	73
Female	16	22	12	17	67
	28	32	45	35	140

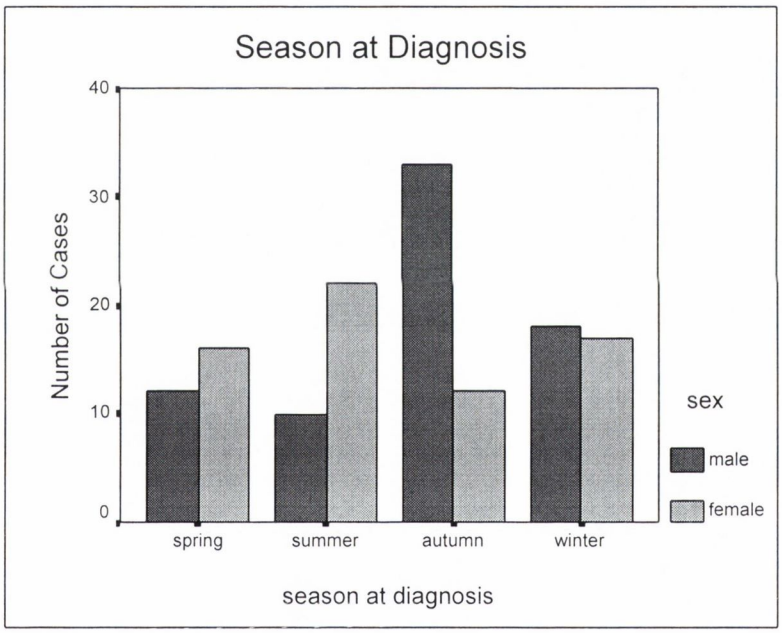

Figure 3.8 Season at Diagnosis by sex

When analysed by age category, the most frequent season of diagnosis in the 10-14.99 year age category was autumn (23) accounting for 42.6% of cases, with 18.5%, 18.5% and 20.4% in the remaining three seasons (see table 3.6 page 73).

Winter was the most frequent season of diagnosis in the 5-9.99 year age category with 33.9% of diagnoses. The remaining cases were equally distributed among the three other seasons.

In the 0-4.99 year age category, Summer (9) and Autumn (9) were the most frequent seasons of diagnosis, each accounting for 33.3% of cases. The lowest number of cases were diagnosed in Spring (4) at 14.8% and 18.5% in Winter (5).

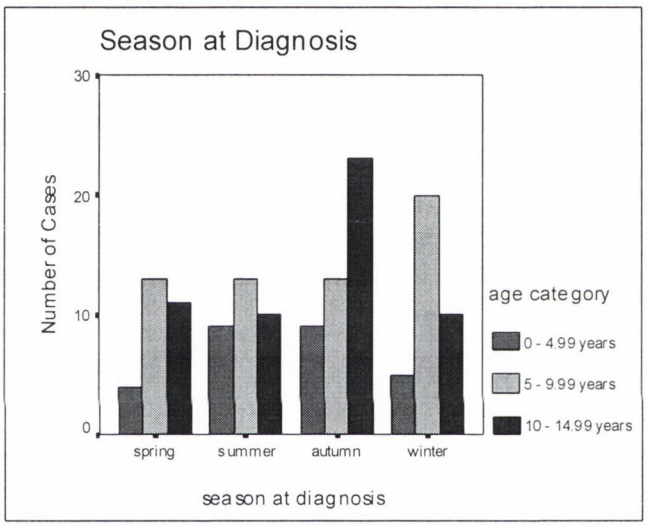

Figure 3.9 Season at diagnosis by age category

Table 3.6 Season of Onset of Diabetes by Sex and Age Category

Age Category	Spring	Summer	Autumn	Winter	Total
0 – 4.99	4	9	9	5	27
male	1	2	6	3	12
female	3	7	3	2	15
5 – 9.99	13	13	13	20	59
male	5	5	10	9	29
female	8	8	3	11	30
10 – 14.99	11	10	23	10	54
male	6	3	17	6	32
female	5	7	6	4	22
	28	32	45	35	140

When examined by age category and sex, a seasonal effect appears more marked for the older age group and particularly for males.

3.9 Month of Diagnosis

The highest number of cases was diagnosed in October, with 20 new cases or 14.3% of the total cases presenting in this month. The lowest number of new cases diagnosed in a month, was 5 cases (3.6%) recorded in April.

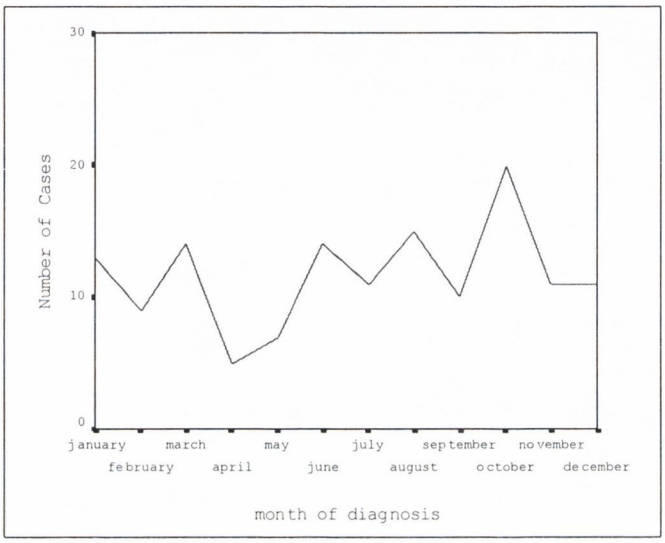

Figure 3.10 ***Frequency of Cases by Month of Diagnosis***

In males, the highest number of cases were diagnosed in October (17.8%) and August (16.4%). There were no new cases diagnosed in boys in April and low numbers in both, May (4.1%) and June (2.7%). In females, the highest number of new cases were recorded in June (17.9%) and the lowest numbers in September(3%) and August (4.5%).

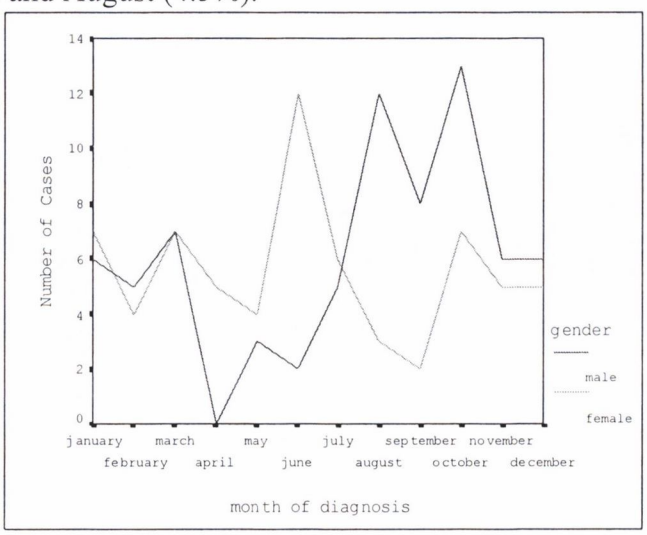

Figure 3. 11

Frequency of cases by month of diagnosis –male and female

The number of new cases presenting per month for each sex and the sexes combined are shown in Table 3.7.

Table 3. 7 Month of diagnosis of Diabetes by sex

Month of Diagnosis	Total Number of Cases (%)	Males	Females
January	13(9.3%)	6(8.2%)	7(10.4%)
February	9 (6.4%)	5(6.8%)	4(6%)
March	14(10%)	7(9.6%)	7(10.4%)
April	5(3.6%)	0	5(7.5%)
May	7(5%)	3(4.1%)	4(6.0%)
June	14(10%)	2 (2.7%)	12(17.9%)
July	11(7.9%)	5(6.8%)	6(9.0%)
August	15(10.7%)	12(16.4%)	3(4.5%)
September	10(7.1%)	8(11%)	2(3.0%)
October	20(14.3%)	13(17.8%)	7(10.4%)
November	11(7.9%)	6(8.2%)	5(7.5%)
December	11(7.9%)	6(8.2%)	5(7.5%)
Total	140 (100%)	73(100%)	67(100%)

Analysis of month of diagnosis by age category

The monthly pattern of diabetes onset varied among the three age categories: 0-4.99; 5-9.99; and 10-14.99 years.

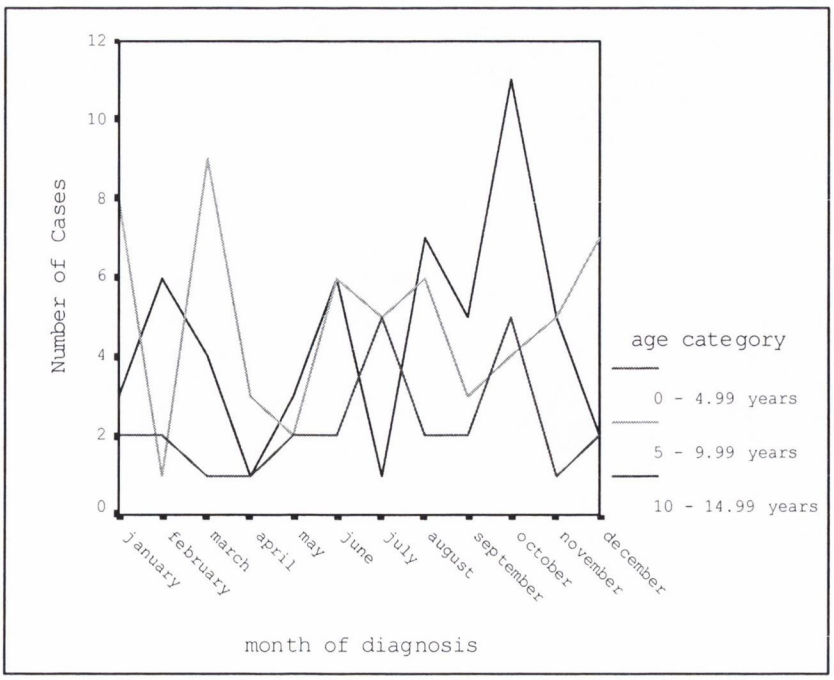

Figure 3.12 Month of diagnosis of diabetes by age category

In those aged under 5 years the most frequent months of diagnosis were July (5 cases) and October (5 cases), 37% of total cases in this age group were diagnosed in these two months. In the remaining 10 months 1-2 cases were diagnosed each month.

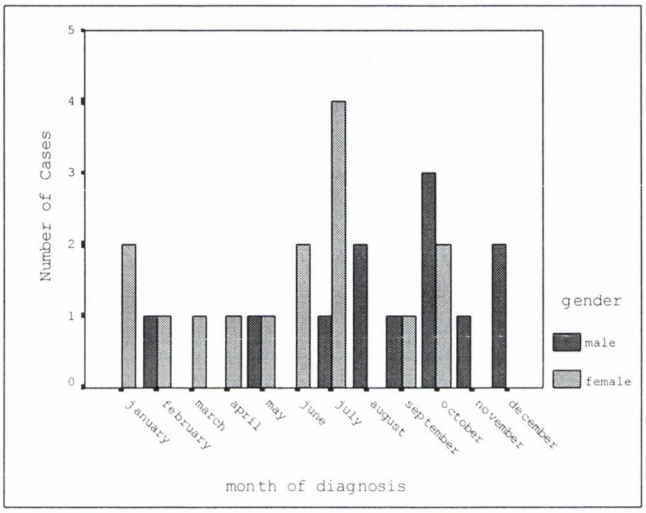

Figure 3.13 Month of diagnosis in the age category 0-4.99, male and female

In those aged 5 – 9.99 years at diagnosis 28.8% of the total cases were diagnosed in January (8cases 13.5%) and March (9 cases 15.2%). The lowest number of cases in this age category were diagnosed in February (1 case, 1.7%).

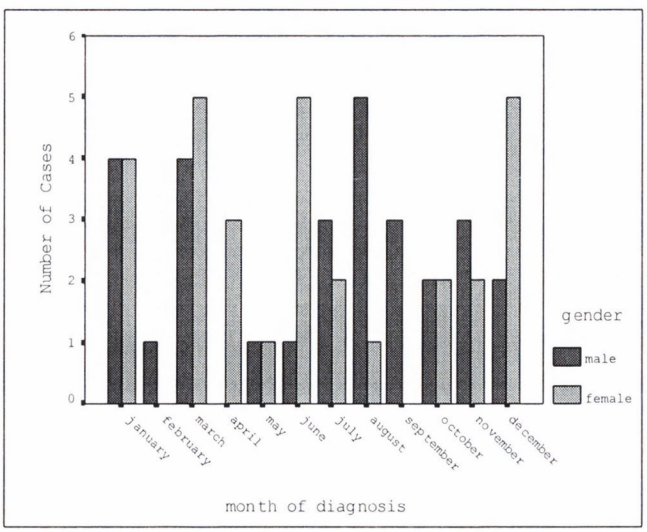

Figure 3.14 Month of diagnosis in the age category 5-9.99, male and female

In the age category 10 – 14.99 years, the highest number of cases were diagnosed in October (11), with 20% of the total cases recorded in this month. The lowest number of cases were noted in the months of April and July, with a single case (1.9%) being notified in each of these months.

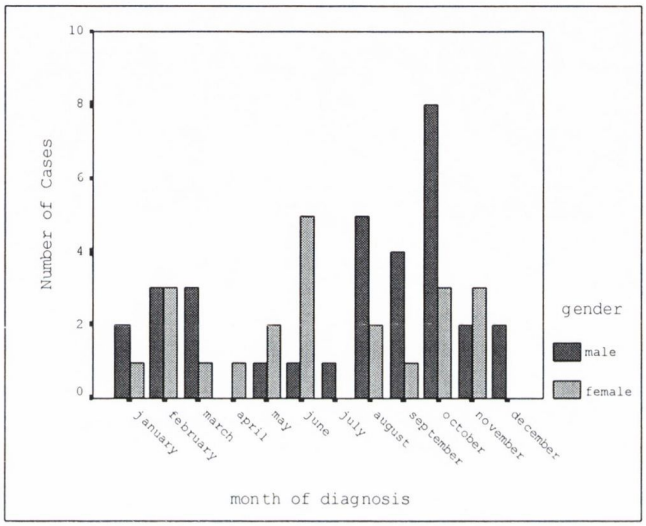

Figure 3.15 Month of diagnosis in the age category 10-14.99, male and female

Table 3.8 Number of Cases diagnosed by month and age category

Month	Total No. of Cases (%) 0-4.99 years			Total Number of Cases (%) 5-9.99			Total Number of Cases (%) 10-14.99		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
January	0	2	2 (7.4%)	4	4	8 (13.6%)	2	1	3 (5.5%)
February	1	1	2 (7.4%)	1	0	1 (1.7%)	3	3	6 (11.1%)
March	0	1	1 (3.7%)	4	5	9 (15.2%)	3	1	4 (7.4%)
April	0	1	1 (3.7%)	0	3	3 (5.1%)	0	1	1 (1.8%)
May	1	1	2 (7.4%)	1	1	2 (3.4%)	1	2	3 (5.5%)
June	0	2	2 (7.4%)	1	5	6 (10.2%)	1	5	6 (11.1%)
July	1	4	5 (18.5%)	3	2	5 (8.5%)	1	0	1 (1.8%)
August	2	0	2 (7.4%)	5	1	6 (10.2%)	5	2	7 (13%)
September	1	1	2 (7.4%)	3	0	3 (5.1%)	4	1	5 (9.3%)
October	3	2	5 (18.5%)	2	2	4 (8.0%)	8	3	11 (20.4%)
November	1	0	1 (3.7%)	3	2	5 (8.5%)	2	3	5 (9.3%)
December	2	0	2 (7.4%)	2	5	7 (11.9%)	2	0	2 (3.7%)
Total	12	15	27	29	30	59	32	22	54

3.10 Seasonality

Log linear analysis was employed to investigate the following effects of age, sex and season of onset of diabetes. The results suggested that the following effects were important: age; sex; and sex by season. This means that there is evidence to suggest that the numbers in different age categories and the pattern over seasons is different for each sex. However, this is a crude analysis of association between variables.

The standard Chi-square Test does not have sufficient power to assess seasonal variation. Assessment of seasonality was made using the Edwards (1961) and Roger test (1977). Roger's test provides a Chi-square statistic on 2 degrees of freedom, it is more reliable than Edward's test in small samples. The method assumed a sinusoidal pattern over the twelve months of the year with a peak and nadir 6 months apart. This method also provides estimates of the timing of the peak and the relative amplitude of the seasonal component. Neither Edward's nor Roger's test achieved statistical significance ($\chi^2 = 4.16$;df=2;p=0.12 and χ^2 =3.65;df=2; p=0.16 respectively). However, there was a fitted peak in October with an amplitude of 24.4%(see figure 3.16). The small numbers in the study did not permit analysis by age category with these tests.

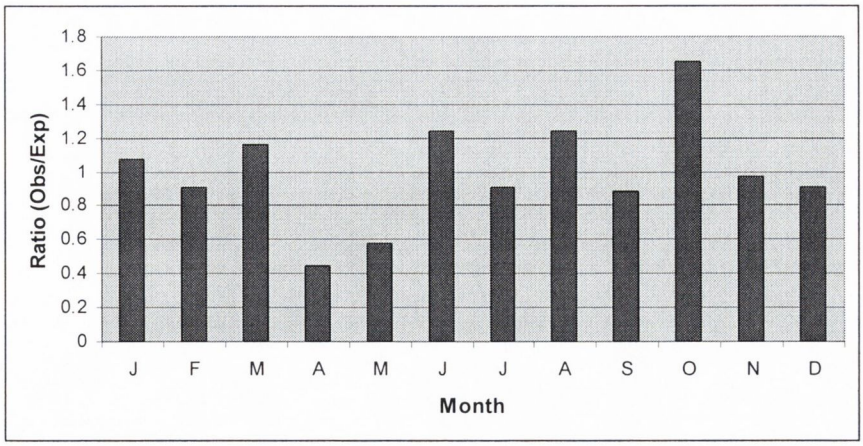

Figure 3.16 Ratio of Observed to expected cases of diabetes by month of diagnosis

3.11 Infant Diet

Data is limited regarding infant diet as these questions were poorly answered. Health professionals not families completed the questionnaires and the required information regarding feeding was often not available. Direct contact with patients and their families was not permitted. The data available is presented in sections 3.11.1 – 3.11.4, however, no useful conclusion can be drawn from such small returns.

3.11.1 Method of Feeding

Information regarding breast-feeding was available on 22.1%. 7 cases were breast fed or 22.6%. 24 cases were bottle fed from birth (77.4%). The maximum number of cases breast fed by year of birth in any one year was 2 cases in 1988.

Information was available on the duration of exclusive breast-feeding for 6 of the 7 breast-fed cases, which ranged from 3 weeks (2 cases) to 6 months (2 cases). A further two children were breast fed in infancy for one month and six weeks respectively. The mean duration of breast-feeding was 2.7 months.

3.11.2 Age of Introduction of Cow's Milk

Information was available regarding the age of introduction of cow's milk in 10% or 14 cases. The earliest age at which cow's milk was introduced was 6 months (3 cases). In the remainder of cases the ages were: 11 (2 cases); 12 (5 cases); 14 (1 case); 15 (1 case) and 18 (2 cases) months. The mean age at which cow's milk was introduced was 11.8 months.

Table 3.9 *Age of Introduction of Cow's Milk*

Age in Months	Frequency	Percent
6	3	21.4%
11	2	14.3%
12	5	35.7%
14	1	7.1%
15	1	7.1%
18	2	14.3%
Total	14	100.0%

3.11.3 Age of Introduction of Solid Foods

Data is available regarding the time of weaning to solid food on 12.1% (17 cases). The time at which solid foods were introduced ranged from 7 weeks to 7 months, the mean age was 4.3 months.

Table 3.10 *Age of introduction of solid foods*

Age in Months	Frequency	Percent
1.75	1	5.9%
3.00	4	23.5%
3.50	1	5.9%
4.00	5	29.4%
5.00	1	5.9%
6.00	2	11.8%
7.00	2	11.8%
Total	17	100.0%

3.11.4 Age of Introduction of Fruit Juice and Sugar to the Diet

Data was available about the age of introduction of fruit juices and sugar to the diet in only 5.7% (8 cases). Fruit juices were introduced to the diet from 7 weeks to 30 months, the mean age being 7.6 months. Sugar was added to the diet from 3.5 to 18 months. The mean age of the addition of sugar was 9.4 months. In one child sugar and fruit juices were never included in the diet.

Table 3.11 *Age of Introduction of Fruit Juice*

Age in Months	Frequency	Percent
never	1	12.5%
1.75	1	12.5%
2.00	1	12.5%
4.00	1	12.5%
5.00	1	12.5%
6.00	1	12.5%
12.00	1	12.5%
30.00	1	12.5%
Total	8	100.0%

Table 3.12 *Age of Introduction of Added Sugar*

Age in Months	Frequency	Percent
never	1	12.5%
3.5	1	12.5%
6.0	1	12.5%
12.0	4	50.0%
18.0	1	12.5%
Total	8	100.0%

3.12 Family History of Diabetes

Information regarding family history of diabetes was available for 117 (83.6%) of the total 140 cases. 2 patients (1.4%) were adopted and so family history was unknown. In one case the type of diabetes was not stated, that is, whether it was

insulin- or non-insulin-dependent diabetes. In 3 cases (2.1%) it was not possible to establish the relationship of the affected family member to the proband.

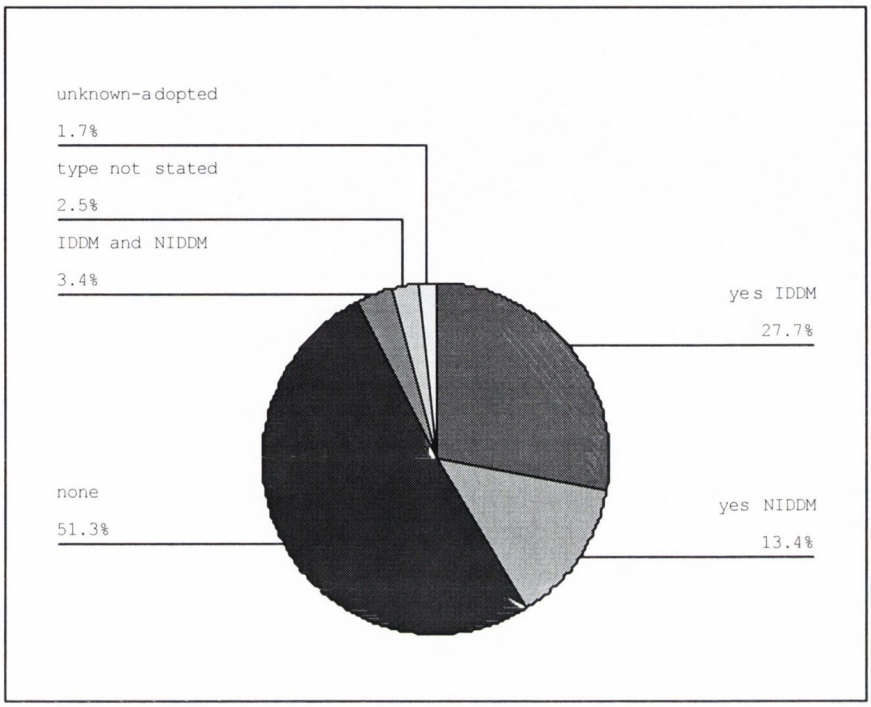

Figure 3.17 *Family history of diabetes*

47% or 56 cases had a family history of diabetes.

Table 3.13 **Family history of diabetes**

Family History of Diabetes	Male	Female	Total
IDDM	15	18	33
NIDDM	8	8	16
IDDM & NIDDM	1	3	4
None	37	24	61
Type not stated	1	2	3
Unknown- adopted	2	0	2
Total	64	55	119

31.6% cases (37) had a positive family history of insulin-dependent diabetes in either a first or second degree relative and 64.7%(n=77) had not.

88.4% (n=99) of patients had no family history of diabetes in a first degree relative. A positive family history of type 1 (insulin-dependent) diabetes in a first degree relative was found in 11.6% (13 cases). The 1st degree relative with insulin-dependent diabetes was: a sibling in 6 cases (46.1%); the child's father in 5 cases (38.5%); and the mother in 2 cases (15.4%). In 6.2% of cases a parent had type 1 (insulin-dependent) diabetes.

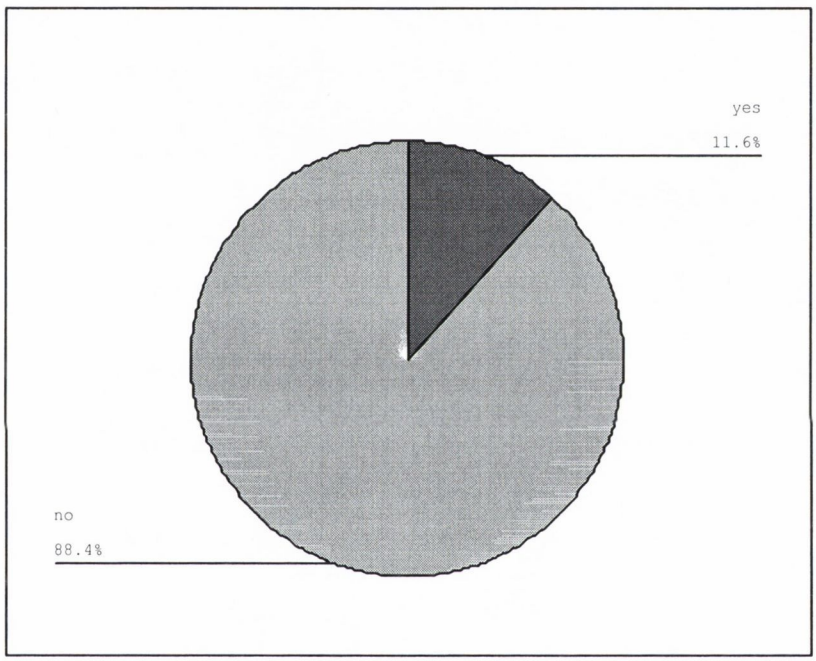

Figure 3.18 Family history of insulin-dependent diabetes in a 1st degree relative

21 patients (17.6%) had a positive family history of insulin-dependent diabetes in a 2nd degree relative. The second degree relative with insulin-dependent diabetes was: an uncle; an aunt; a cousin; a grandparent.

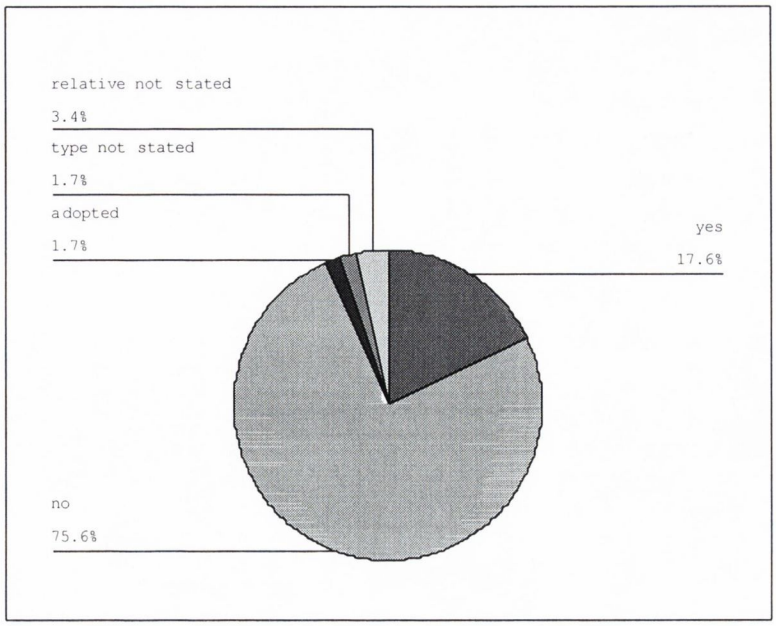

Figure 3.19 Family history of insulin-dependent diabetes in a 2nd degree relative

There was no significant difference between those who had a positive family history of insulin dependent diabetes in a first degree relative and the age category at diagnosis (χ^2=2.9;df=2; p = 0.226).

Table 3.14 *Family history of insulin-dependent diabetes in a 1st degree relative by age category at diagnosis*

Family History IDDM in 1st Degree Relative	Yes	No	Total
0-4.99 years	5	20	25
5-10 years	3	43	46
10-15 years	5	36	41
	13	99	112

No difference was found between males and females in the occurrence of a positive family history of insulin dependent diabetes (χ^2=5.7; df=5; p=0.358).

Table 3.15 *Family history of insulin-dependent diabetes in a 1st or 2nd degree relative by sex*

Family History of IDDM		Sex		Total
		Male	Female	
1st degree relative	Yes	5	8	13
2nd degree relative	Yes	9	12	21
1st degree relative	No	53	46	99
2nd degree relative	No	50	40	90

17.1% (20 cases) had a family history of type 2, non-insulin-dependent diabetes. In 4 cases there was also a family history of type 1 diabetes. In 13 cases (65%) a grandparent had type 2 diabetes, in 4 cases (20%) an uncle, in 2 case (10%) an aunt and in 1 case (5%) there was a family history of type 2 diabetes in both grandparents, an uncle and an aunt.

3.13 Birth Order

Information regarding birth order was available on 85/140 (60.7%). Of those on whom data is available 38.8% of cases were firstborn children, the remainder were 2nd (30.6%); 3rd (17.6%); 4th (7.1%); and 6th (5.9%) born children respectively.

Table 3.16 ***Birth Order and Age Category at Diagnosis***

Age Category at Diagnosis (years)	Birth Order					
	1st	2nd	3rd	4th	6th	total
0-4.99	8	7	3	2	3	23
5-9.99	19	12	5	1	0	37
10-14.99	6	7	7	3	2	25
Total	33	26	15	6	5	85

There was no significant difference between birth order and age category at diagnosis (χ^2=11.57; df=8; p=0.169). There was no significant difference between birth order and sex (χ^2=3.64; df=4; p=0.471). There was no significant difference between being firstborn or second-born (χ^2=0.831; df=1; p=0.362).

3.14 Family Size

Data regarding the number of occupants in the home was available on 101 of the total 140 (72%) cases. The number of occupants in the home ranged from 3 to 9 with a median of 5. The mean number of occupants was 4.91. A third had (33 cases) 4 occupants in the home, 31% cases had 5 occupants (n=31) and 25%(n=25) of cases had 6 or more occupants in the home.

There was a significant association between the age category at diagnosis and the number of occupants in the home (χ^2=23.4; df 12; p = 0.009). There was a significant association (χ^2=11.33; df 2; p = 0.003) between age category at diagnosis and less than five occupants in the home.

3.15 Number of Siblings

Information is available regarding the number of siblings for 99 of the 140 cases (71%). The number of siblings varied from none to six. 61.6% had 1 or 2 siblings (see table 3.17).

Table 3.17 ***Number of Siblings***

Number of Siblings	Frequency	Percent
0	10	10.1%
1	33	33.3%
2	28	28.3%
3	13	13.1%
4	7	7.1%
5	7	7.1%
6	1	1.0%
Total	99	100.0%

3.16 Presenting Clinical History

Information is available regarding presenting symptoms on 111 of the total 140 cases (79.3%), displayed in table 3.17. Of those who responded 93.7% reported polyuria and polydipsia (74.3% of total), 2.1% reported polyuria alone and 2.9% reported no polyuria/polydipsia. Weight loss was reported to have occurred in 40.7%. Eneuresis was reported to have occurred in 14.3% of total replies and nocturia in 5%. Other symptoms reported include lethargy (14.3%), vomiting (5%), anorexia (2.1%), abdominal pain (2.1%), recurrent infections(2.1%), vulval pruritus or candida(2.1%), increased appetite(1.4%), constipation (1.4%), headache, "strong smell from the nappies", family blood glucose check, generalised pruritus all 0.7%. The diagnosis was reported as an incidental finding in 2 cases (1.4%).

Table 3.18 ***Presenting Symptoms***

Presenting Symptom	Frequency	Percent Replies	Percent of Total
Polyuria/polydipsia	104	93.7%	74.3%
Polyuria	3	2.7%	2.1
Eneuresis	20	37.7	14.3
Nocturia	7	13.2	5.0
Dysuria	1	1.9	0.7
Weight loss	57	65.5	40.7
Lethargy	20	40.8	14.3
Vomiting	7	14.3	5.0
Recurrent infections	3	6.1	2.1
Vulval pruritus/candida	3	6.1	2.1
Anorexia	3	6.1	2.1
Abdominal pain	3	6.1	2.1
Blurring of vision	3	6.1	1.4
Increased appetite	2	4.1	1.4
Constipation	2	4.1	1.4
Incidental	2	4.1	1.4
Pruritus	1	2.0	0.7
Headache	1	2.0	0.7
Strong smell from nappies	1	2.0	0.7
Family bg check	1	2.0	0.7%

3.16.1 Presenting Symptoms by Age Category

In those aged 0 – 4.99 years, data is available regarding symptoms on 25 cases (93%). The most frequent symptoms were: polyuria and polydipsia in 21 cases (77.8% total age category); polyuria alone in 2 cases (7.4%) and weight loss in 9 cases (33.3%). Eneuresis was reported in 5 cases (18.5%) and nocturia in 1 case (3.7%).

Other symptoms reported included vomiting was reported in 4 cases (14.8%), constipation in 2 cases (7.4%) and lethargy, recurrent infections, anorexia, and a "strong smell" from the nappies in 1 case respectively (3.7% total age category).

In the age category 5 –9.99 years, data is available regarding symptoms on 46 cases (78%). The most frequent symptoms reported were: polyuria and polydipsia in 43 cases (72.9% total age category), polyuria alone in 1 case (1.7%) and weight loss in 23 cases (39%). Additional urinary symptoms were reported including eneuresis in 14 cases (23.7%), nocturia in 3 cases (5.1%) and dysuria in 1 case (1.7%). Other complaints include lethargy in 10 cases (16.9%), vulval pruritus or candida in 2 cases (3.4%), increased appetite in 2 cases (3.4%), abdominal pain in 2 cases (3.4%), vomiting in 1 case (1.7%), pruritus in 1 case (1.7%) and recurrent infections in 1 case (1.7%). In one case the diagnosis was suggested by a family blood glucose (1.7%) and in 2 cases the diagnosis was incidental (3.4%).

In those aged 10 – 14.99 years, data is available regarding symptoms on 40/54 cases (74.1%). The most frequent presenting symptoms were polyuria and polydipsia in 40 cases (74.1% total age category), weight loss in 25 cases (46.3%), and lethargy in 9 cases (16.7%). Additional urinary symptoms included eneuresis in 1 case (1.9%) and nocturia in 3 cases (5.6%). Other symptoms reported were blurred vision in 3 cases (5.6%), vomiting in 2 cases (3.7%), anorexia in 2 cases (3.7%), vulval pruritus and candida in 1 case (1.9%), abdominal pain in 1 case (1.9%), recurrent infections in 1 case (1.9%) and headache in 1 case (1.9%).

3.16.2 Diabetic Ketoacidosis at Presentation

The definition of diabetic ketoacidosis used was: blood glucose > 15 mmol, urinary ketones +2, pH < 7.2, HCO_3^- < 15 mmol and clinical symptoms. 26 cases (18.6% of total) were reported to be in DKA at presentation, 70 cases (50%) were not in DKA and a further 6% were treated as DKA but did not fulfil the above criteria. Data is not available on the remaining 35 cases (25%).

In those aged 0 – 4.99 years, 6 cases (25%) were in DKA at presentation. A further 2 cases (8.3%) were treated as having DKA but did not fulfil the criteria. 16 cases (66.7%) were confirmed not to have DKA at presentation. Data is not available on the remaining 3 cases (11.1% of the total age category).

In those aged 5.99 – 10 years, 12 cases (27.3%) were in DKA at presentation. A further 3 cases (6.8%) were treated as having DKA but did not fulfil the criteria.

28 cases (63.6%) were confirmed not to have DKA at presentation. Data is not available on the remaining 16 cases (27.2% of the total age category).

In those aged 10 – 14.99 years, 8 cases (21.1%) were in DKA at presentation. A further 4 cases (10.5%) were treated as having DKA but did not fulfil the criteria. 26 cases (68.4%) were confirmed not to have DKA at presentation. Data is not available on the remaining 16 cases (29.6% of the total age category).

There was no significant association between the age category at diagnosis and presentation in severe diabetic ketoacidosis (χ^2=0.7; df=4; p =0.949).

3.16.3 Duration of Symptoms

Information available on 112(80%) of the total 140 cases. The median duration of symptoms was 14 days. The inter-quartile range was 15 days. The mean duration of symptoms was 18.24 days with a range of 0- 180 days.

When analysed by age category at diagnosis, those aged 0-4.99 years had a median duration of symptoms of 7 days, the inter-quartile range was 10.5 days and mean duration of symptoms was 9.7 days, range 1-35days. Those aged 5-9.99 years had a median duration of symptoms of 14 days. The inter-quartile range was 14 days, the mean duration of symptoms 20.0 days and the range 0-180 days. Those aged 10-14.99 years, had a median duration of symptoms of 14 days. The inter-quartile range was 24.3 days, the mean duration of symptoms was 21.7 days with a range of 2-120days.

There was a significant difference in the duration of symptoms when analysed by age category (The Kruskal-Wallis Chi-square=7.67;df=2;p=0.022). The duration of symptoms was shortest in the youngest age category.

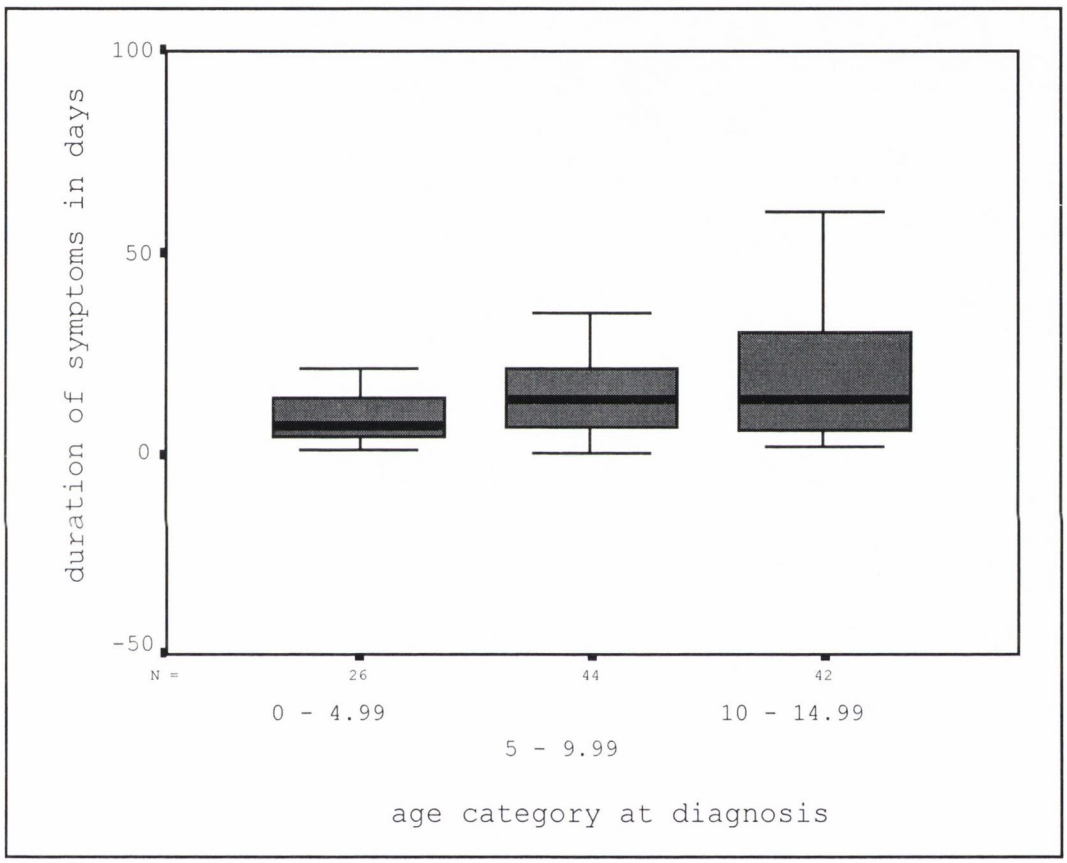

Figure 3.20 ***Boxplot Duration of symptoms by age category***

CHAPTER FOUR

DISCUSSION

4. DISCUSSION

4.1 Introduction

Insulin dependent diabetes mellitus is a common chronic disease of childhood. It is a condition associated with significant morbidity and premature mortality. It is a condition which consumes a significant proportion of healthcare resources. The results of the Diabetes Control and Complications Trial (1993) shows that good glycaemic control of diabetes reduces the occurrence of long term complications. As a result health care providers require accurate information regarding the frequency of this disease in their population so that they can plan and provide appropriate services to those with diabetes. These services should aim to maximise quality of life and reduce the occurrence of disease related complications. The societal costs of diabetes extend beyond the economic burden to the healthcare sector. The complications of diabetes result in reduced quality of life, often an inability to work and live independently thereby placing a further economic burden on the Exchequer. The ability to plan appropriate services depends on the availability of accurate information regarding the occurrence of disease in a population. To date no accurate information has been available regarding the frequency of this disease in the Irish population. This study sought to provide this information and has been met with enthusiasm by the health policy planners in the Irish Department of Health and Children.

4.2 Source of Incident Cases

In this study, the majority of new cases of diabetes were reported by Paediatricians. This reflects the referral patterns in this age group and would be anticipated. A good response was received from the initial survey through the Irish Paediatric Surveillance Unit (IPSU), the IPSU response rates are outlined in Appendix III. Further follow-up of non-responders by letter and telephone yielded a further 37 cases. Of the 142 cases initially identified two cases had cystic fibrosis as a primary condition and so these cases were excluded from the analysis. One report could not be confirmed despite exhaustive attempts and was excluded from the analysis.

All but one Irish Paediatrician provided data to this study, reflecting a 98.6% response rate. All hospitals in the State were contacted to ensure no cases had been missed. The response rate from individual physicians was 71%. A further 11 cases were identified from adult physicians, endocrinologists and diabetes nurse specialists.

4.3 Age Category at Diagnosis

There was a significant difference in the age category at diagnosis, with a lower number of cases than expected diagnosed in the 0 – 4.99 year age category. Green et al, 1992 also found the incidence rates in this age group to be the lowest in most areas of Europe, as did Patterson et al (2000) in a more recent study of 44 centres in Europe by the EURODIAB ACE study group. This study showed

the highest incidence in the 10-14 year age group but noted the highest rate of increase in those aged 0-4 years at 6.3%. In Ireland, the highest number of cases was diagnosed between 5 and 9.99 years. This is similar to the experience in Italy (Cherubini et al, 1994). However, this differs from the experience in most areas of Europe where the peak has appeared in the 10-14 age group (Green et al, 1992).

4.4 Sex

There was a slight excess of male cases overall but this did not reach statistical significance, as in most other studies. The male to female ratio of cases was 1.09:1. The ratio of males to females in the general population under the age of 15 years was 1.06:1. This is in keeping with the results from other studies where areas of high incidence of diabetes tend to show a slight male preponderance, which often does not reach statistical significance. This male excess has been demonstrated in Finland, Sardinia, Norway (Green et al, 1992) and the British Isles (Bloom et al, 1975). In the study by Joner et al (1981), there was a significantly higher incidence noted in Norweigan males.

When examined by age category there was a slight female excess of cases in the two younger age categories but a male excess in the 10 –14 year age group. Bloom et al (1975), in the British Isles showed a slight male excess in the age groups 0 -4 and 11 - 15 years, and a female excess from 5-10

years. Rewers et al (1988), suggests that diabetes often shows a slight male preponderance in Caucasians as demonstrated in this study.

In contrast, areas of low diabetes incidence often have a slight female excess. This has been shown in studies from Romania, Israel, and Poland (Green et al, 1992), Hungary, Lithuania, Latvia and Japan (Soltesz et al, 1992).

4.5 Incidence Rates

The overall crude incidence rate of diabetes, in Ireland, in those aged under 15 years in 1997 was calculated at 16.6 per 100,000 per year (95% confidence interval 13.7 – 19.2). This suggests that Ireland has a high incidence of diabetes and not a low incidence as previously reported (Bloom et al, 1975), (Metcalfe and Baum, 1991). This is the first study on the incidence of diabetes in Ireland performed in Ireland. Two previous studies performed in the British Isles have included Irish data. The study by Bloom et al (1972), suggested a lower incidence of diabetes in Ireland when compared to the rest of the British Isles. They reported an incidence rate of 7.67 per 100,000 for the British Isles but only reported 51 cases from Ireland equivalent to 4.43 notification per 100,000. No measure of ascertainment was provided in this study and the apparent low incidence in Ireland was probably due to under-reporting of cases. The study by Metcalfe and Baum (1991), in children under 15 years in the British Isles during 1988, reported an overall incidence rate of 13.5 per 100,000 per year (95% CI 12.9– 14.2). This study also reported a low incidence rate for Ireland at 6.8 per

100,000 per year but again no measure of case ascertainment was provided in this study for Ireland and there is concern that the data could be incomplete giving an apparently low incidence for Ireland.

4.5.1 International Comparison of Incidence Rates of Diabetes

The value of reporting crude incidence rates is that they describe the actual experience of the population which they represent and so are of great value for health service providers. However, it is not valid to compare crude incidence rates of different populations as crude rates fail to compensate for underlying differences in population structure. International comparison of incidence rates of disease is only possible if either category specific rates are compared or if incidence rates are standardised. It is difficult to compare multiple category specific rates when comparing incidence data among a large number of countries and so presentation of standardised incidence rates are more appropriate. The standardised incidence rate, using the direct method of standardisation, for those aged less than 15 years is 16.3 per 100,000 per year (95% confidence interval 14.2-18.5). The standardised incidence rate for males under 15 years is 16.4 per 100,000 per year (95% CI 13.2-21.1) and the standardised incidence rate for females under 15 years is 16.2 per 100,000 per year (95% CI 12.6-20.7). When compared with international data from the EURODIAB ACE study, where the same method of standardisation was employed, Ireland is shown to have a high incidence of diabetes. Irish data has been inserted into Table 4.1 to demonstrate the incidence rate in Ireland relative to other countries. It must be remembered that this data relates to the years 1989-90 and the incidence rate in these

countries is likely to have increased since the time of study. However, the value of this comparison is that male and female standardised incidence is presented.

Table 4.1

Comparison of standardised incidence rates of diabetes in Ireland and Europe (1989-90) by sex

Country (region)	Boys Rate* (95% C.L.)	Girls Rate* (95% C.L.)	All Rate* (95% C.L.)
Greece (Northern)	5.3(2.4,10.1)	3.8(1.4,8.2)	4.6 (2.6,7.5)
Romania (Bucharest region)	4.6(2.9,6.9)	5.7(3.7,8.4)	5.1 (3.8,6.8)
Poland (9 western provinces)	5.3(4.6,6.5)	5.8(4.6,7.2)	5.5 (4.7,6.4)
Israel (whole nation)	4.4(3.4,5.6)	6.7(5.4,8.2)	5.5 (4.7,6.5)
Poland (3 cities)	5.7(4.2,7.5)	6.0(4.5,7.9)	5.8(4.8,7.1)
Slovenia	5.2(3.3,10.4)	7.7(5.3,10.9)	6.5(4.9,8.4)
Italy (Lazio region)	7.2(5.5,9.1)	5.8(4.4,7.7)	6.5(5.4,7.8)
Italy (Lombardia region)	7.6(6.3,9.2)	5.9(4.7,7.3)	6.8(5.8,7.8)
Portugal (3 regions combined)	10.1(5.9,16.1)	4.9(2.1,9.6)	7.5 (4.8,11.0)
Hungary (18 counties)	7.7(6.4,9.1)	7.5(6.3,9.0)	7.6(6.7,8.6)
Austria(whole nation)	7.9(6.5,9.3)	7.5(6.1,9.2)	7.7 (6.7,7.8)
France (4 regions)	7.8(6.6,9.3)	7.8(6.5,9.2)	7.8 (6.9,8.8)
Greece(Athens region)	10.9(8.5,13.7)	7.7(5.7,10.2)	9.3(7.7,11.1)
Belgium (Antwerp region)	9.2 (5.2, 15.3)	10.4 (5.9,16.9)	9.8 (6.7, 13.9)
Italy (eastern Sicily)	11.2(7.5,16.1)	9.0(5.7,13.5)	10.1(7.5,13.2)
Spain (Catalonia region)	10.5(8.8,12.3)	10.6(9.0,12.5)	10.6(9.4,11.9)
Netherlands (5 regions)	11.2(7.6, 16.0)	10.8(7.2,15.7)	11.0(8.4,11.3)
Luxembourg (whole nation)	12.1(5.2,23.9)	12.6(5.4,24.8)	12.4(7.1,20.1)
Ireland (whole nation)	**16.4(13.5,19.4)**	**16.2(13.2,19.3)**	**16.3(14.2,18.5)**
UK (Oxford region)	17.8(14.3,21.9)	14.9(11.7,18.8)	16.4(13.9,19.1)
UK (Northern Ireland)	17.8(13.9,22.5)	15.4(11.7,19.8)	16.6(13.9,19.7)
Norway (8 counties)	22.3(17.9,27.6)	19.3(15.1,24.3)	20.8(17.7,24.3)
Denmark (3 counties)	21.5(14.9,30.1)	21.4(14.7,30.3)	21.5(16.6, 7.3)
Italy (Sardinia)	33.5(27.9,39.9)	26.9(21.7,32.9)	30.2(26.4,34.4)
Finland (2 regions)	47.0 (37.5,58.1)	38.8(30.5,50.0)	42.9(36.3,50.6)

*number of cases per 100,000per year

Adjusted from Eurodiab Ace data *Incidence of childhood-onset insulin-dependent diabetes mellitus: the Eurodiab Ace study – A.Green, EAM Gale, CC Patterson , The Lancet Vol 339 April, 1992, 905-909.*

The standardised incidence rate of diabetes in Ireland is also similar to that reported in other areas of the British Isles such as Oxford at 16.4 per 100,000 (95% confidence interval 13.9-19.1) (Bingley and Gale, 1989) and Northern Ireland 16.6 per 100,000 (95% confidence interval 13.9-19.7) (Green et al, 1992).

The most recent published incidence data from Europe relating to the years 1989 to 1994 from the EURODIAB Ace study group (2000), again confirms the Irish incidence to be high when compared with data from other European countries. The standardised incidence rates of insulin dependent diabetes in those aged under 15 years presented in this study for the British Isles, are:
Northern Ireland at 19.6 (17.8–21.4) for the time period 1989-1994; Leeds at 15.7 (14.5–16.9) for the same period; and Leicestershire at 15.9 (13.5–18.3) for the period 1989-93. The standardised incidence rate presented for the Oxford region is 17.6 (16.1-19.1), the period of study is not specified. The standardised incidence rate of insulin dependent diabetes in those aged under 15 years in Ireland, using the same method of standardisation, at 16.3 per 100,000 per year (14.2-18.5) is similar to that from other areas of the British Isles.

In other areas of Europe the EURODIAB ACE study (2000) presents standardised incidence rates of 3.2(2.5-3.8) for Macedonia, 6.2 (4.5-8.0) for Northern Greece, 8.3(7.8-8.9) for France, 13.0(11.8-14.3) for the Netherlands, 16.0(13.9-18.1) for Denmark, 36.6(33.9-39.4) for Sardinia and 40.2(36.4-44.1) for two regions of Finland. In this study of 44 centres from Europe, 34(77%) have recorded incidence rates below 15.0 per 100,000 per year while only

10(23%) centres have reported a standardised incidence rate above 15.0 per 100,000 per year. This would suggest that Ireland does have a moderately high incidence of diabetes and not a low incidence.

It is true that the Irish data presented relates to a later period of study than the incidence data presented from these other centres and a secular trend has been described for insulin dependent diabetes in those aged under 15 years in most of Europe. This does limit the ability to directly compare the data. However, if the data from the EURODIAB ACE study (1992), relating to the period 1989-1990, is compared with that of the most recent EURODIAB ACE study (2000), relating to the period 1989 – 1994, the increase in incidence rate has been a modest in most centres. The increased incidence in these time periods is most marked for Northern Ireland and Sardinia. (See table 4.2)

There is no more recent published incidence data available with which to compare the Irish incidence rates and so despite the limitations of comparing slightly different time periods the EURODIAB ACE study published in March 2000, affords the best comparison of this data. Discussions have taken place with a number of leading experts both nationally and internationally regarding the Irish incidence data presented here. In particular discussion has occurred with Dr. Chris Patterson, a key member of the EURODIAB ACE Study Group and holder of the Diabetes Registry in Northern Ireland who felt that the incidence data presented in this study was appropriate. This study provides an effective baseline measurement for monitoring changes in the incidence of this disease in the Irish population.

Table 4.2

Comparison of standardised incidence rates of diabetes in Ireland and Europe (1989-94)

Country (region)	**1989/1990** Standardised rate (95% CL)	**1989-1994*** Standardised rate (95% CL)
Greece (Northern)	4.6 (2.6,7.5)	6.2(4.5,8.0)*
Romania(Bucharest region)	5.1 (3.8,6.8)	5.0(4.1,5.8)*
Poland (9 western provinces)	5.5 (4.7,6.4)	6.7(6.2,7.3) (1991-4) 8western provinces
Israel (whole nation)	5.5 (4.7,6.5)	5.9 (5.3,6.4)(1993)
Poland (3 cities)	5.8(4.8,7.1)	6.1(5.4,6.8)*
Slovenia	6.5(4.9,8.4)	7.6(6.5,8.7) (1992-4)
Italy (Lazio region)	6.5(5.4,7.8)	8.1(7.3,8.9) (1993-4)
Italy (Lombardia region)	6.8(5.8,7.8)	7.0(6.4,7.6)
Portugal (3 regions combined)	7.5 (4.8,11.0)	
Hungary (18 counties)	7.6(6.7,8.6)	8.9(8.2,9.5)*
Austria(whole nation)	7.7 (6.7,7.8)	9.1(8.5,9.8) (1991-94)
France (4 regions)	7.8 (6.9,8.8)	8.3(7.8,8.9) (1991-94)
Greece(Athens region)	9.3(7.7,11.1)	
Belgium (Antwerp region)	9.8 (6.7, 13.9)	11.6(9.4,13.7)*
Italy (eastern Sicily)	10.1(7.5,13.2)	11.4(9.5,13.2) (1991-4)
Spain (Catalonia region)	10.6(9.4,11.9)	12.3(11.4,13.1) (1991-4)
Netherlands (5 regions)	11.0(8.4,11.3)	13.0(11.8,14.3) (1991-4)
Luxembourg (whole nation)	12.4(7.1,20.1)	12.1(8.7,15.5) (1993-4)
Ireland (Republic of Ireland)		**16.3(14.2,18.5) (1997)**
UK (Oxford region)	16.4(13.9,19.1)	17.6(16.1,19.1)
UK (Northern Ireland)	16.6(13.9,19.7)	19.6(17.8,21.4)*
Norway (8 counties)	20.8(17.7,24.3)	21.2(19.3,23.1) (1992-4)
Denmark (3 counties)	21.5(16.6, 7.3)	16.0(13.9,18.1) (1991-4)
Italy (Sardinia)	30.2(26.4,34.4)	36.6(33.9,39.4) (1991-4)
Finland (2 regions)	42.9(36.3,50.6)	40.2(36.4,44.1) (1992-3)

Table constructed from data from the EURODIAB ACE Study Group Green et al (1992) and the EURODIAB ACE Study Group (2000)

4.5.2 Category Specific Incidence Rates

The category specific rates for the Irish population may be compared directly with those of other populations. Category specific rates are available for two other areas of the British Isles in 1989/90, which can be compared given the reservations outlined above.

Table 4.3 Comparison of Category –Specific Incidence Data Ireland and the UK

Country /Region	*No of cases per 100,000 per year*					
	Boys			Girls		
	0-4.9 years	5-9.9 years	10-14.9 years	0-4.9 years	5-9.9 years	10-14.9 years
Ireland	9.3	20.4	19.6	12.4	22.1	14.2
UK (Northern Ireland)*	11.4	15.5	26.5	13.6	13.8	18.7
UK (Oxford region)*	15.2	14.3	23.9	11.3	13.4	20.0

*data derived from EURODIAB ACE (Green et al, 1992)

In this study the highest incidence rates were noted for the 5-9.99 year age category for both males and females. In the two other areas the highest incidence is in the 10-14 year age category. In Northern Ireland the incidence is higher in girls under the age of five years than boys, as in this study. In the two other age categories in Northern Ireland the incidence in boys is higher than girls, in this study the incidence in girls is also higher in the 5-9.99 year age category. In the Oxford region the incidence in boys is higher than in girls in all three age categories.

4.6 Estimate of Ascertainment

In order to provide a measure of case ascertainment in the study a second source of case identification was sought. In choosing a secondary source the criteria are: that it be independent of the first source, that each case has an equal probability of being captured by either source, and that the probability of ascertainment is

constant over time. It is desirable that the second source be computerised. A large number of potential secondary sources were considered.

In Ireland the practice is that children and adolescents with newly diagnosed diabetes mellitus are admitted to hospital. The Hospital In-Patient Enquiry system, or H.I.P.E., as it is known, is a computer based health information system which collects hospital activity data regarding discharges and deaths from acute hospitals by disease category. This was considered as an alternative source of secondary case identification. However, on further evaluation this H.I.P.E. data was not chosen as it had a number of limitations. There are a number of diagnostic codes relating to diabetes but the initial presentation of diabetes does not have a unique code. Thus, using data recorded from the H.I.P.E. system it is only possible to identify the total number of admissions to hospital with diabetes. It is not possible to isolate new cases of diabetes from re-admissions to hospital with diabetes. Attempts can be made to limit the admissions to a single admission episode per patient within a particular hospital but this will not detect admissions to other hospitals. In this study a number of newly diagnosed patients were admitted to one hospital and transferred to another for further management. HIPE data will also not detect those individuals who have been previously diagnosed elsewhere. A further limitation of the HIPE data as a data source for this study is that access to patient names was not possible to apply the capture-recapture technique. A further potential bias in this data is that HIPE data currently relates only to public hospitals so that private patients would be systematically excluded from this data set. The internationally derived H.I.P.E. diagnostic codes, using the International Classification of Diseases, 9th Revision,

relating to diabetes cannot be altered nationally for the collection of incidence data. The HIPE diagnostic codes relating to diabetes are shown in Appendix VI. Data was obtained from the HIPE database for general comparison with the study data, while recognising that this data may represent multiple admissions for a single case (Table 4.4).

Table 4.4 Hospital In-Patient Enquiry Data
Diabetes In-patient Activity age 0-14

1997	Principal Diagnosis	Secondary Diagnosis	Total Cases
25001	41	73	114
25003	106	13	119
Totals	147	86	233

Data supplied from the HIPE Department, The Economic and Social Research Institute, Dublin

Note: Estimated national HIPE coverage in 1997 was 97%.
Activity limited to "1 episode per patient" eliminating re-admissions *within* individual hospitals.

It is unlikely that newly diagnosed diabetes would be considered a secondary diagnosis and so in the study period 147 episodes of admission for diabetes were recorded for 1997 which is similar to that found in this study. The majority of those coding the initial presentation of insulin dependent diabetes will ascribe the code 25003, that is:

"type 1 [insulin dependent type][IDDM][juvenile type], uncontrolled". However, not all institutions will use this code for new onset diabetes.

This study sought to capture all those with type 1 (insulin-dependent) diabetes who would require insulin therapy and so a potential source of data confirmation was a record of insulin prescriptions. Insulin prescriptions are dispensed from a

large number of independent pharmacies throughout the country. These 2,500 independent pharmacies are represented by the Irish pharmaceutical Union and this organisation was contacted to ascertain if there was a record of insulin prescriptions issued or if, individual pharmacies would be willing to furnish data relating to unique insulin prescriptions dispensed in 1997. The Irish Pharmaceutical Union stated that they did not have this information and would not advocate a survey of local pharmacies. The Irish Pharmaceutical Healthcare Association was also contacted in this regard with no success. The major insulin producing pharmaceutical companies were also contacted but did not have appropriate data. The Irish Diabetes Federation, a patient organisation, was also considered but the required patient data was not available.

The centralised government healthcare support schemes for those with diabetes was chosen as the most appropriate secondary source of case ascertainment, as described in Chapter 2. These government schemes are administered by the G.M.S. (Payments) Board. The scheme chosen was the Long-term illness card (LTI) provided to those with diabetes as being most representative and reliable. It must be remembered that data is collected by the G.M.S. (Payments) Board for the purpose of payment and not for epidemiological purposes.

In using this secondary source to validate the study data a number of misclassifications of cases were identified thus, this source while not ideal for this purpose is the best available in Ireland at present. The study data reveals that at least 55% of cases identified by the primary source alone meet the criteria for inclusion in the second source but have not been identified. That these

patients were not identified in the second source is important only as it raises questions about the reliability of the method of coding for diabetes in this data set. As a result, it raises the possibility that, some or all, of the 42 cases (27%) identified by the second source alone may not be totally accurate and may not meet all the criteria of the study namely confirmed diabetes and aged less than 15 years. If a number of cases identified by the second source alone, do not have diabetes or are not aged under 15 years this would result in a falsely low ascertainnment level in the study and an overestimate of the number with diabetes.

Data relating to long-term illness cards is supplied to the G.M.S. (Payments) Board from individual Health Boards, who retain hand-held records, thus requiring multiple re-entry of data and potential transcription error. The code for diabetes is a single letter that may be misread or mistyped easily. The date of birth is similarly subject to multiple data entries. The investigator attempted to acquire data directly from the individual Health Board for verification areas but this request was declined.

The Department of Health and Children and the G.M.S. (Payments) Board were appreciative of the role that this study has fulfilled in providing a check on the accuracy of their data. The Department of Health and Children are attempting to access the core information to refine the data provided by this secondary source. Due to patient confidentiality I am not permitted direct access to this patient data.

However, despite its limitations, the data as presented for the secondary source of ascertainment remains the best available. The cases verified by both sources (n=101) are confirmed. The cases identified by the primary source are accurate (n=140). The number of cases identified by the second source alone (n=52) appears to be an over estimate and thus provides a falsely low ascertainment level in this study and an overestimate of the total number of cases of diabetes.

Applying the capture-recapture technique (section 2.7.5) to the data available, given the reservations outlined above, we find the estimate of the total number of cases of diabetes in the population was 212 (95% confidence interval 199-224). The estimate of ascertainment in the primary source was 66%, in the secondary source was 72.2% and in both sources combined was 90.6%.

We know that the incidence of diabetes is at least that presented in the study and may be slightly higher. Internationally there is a reluctance to provide ascertainment corrected incidence rates as they do not record the actual documented experience of a population. However, if the estimated number with diabetes above were true, this would equate with a crude incidence rate of disease of 25.1 per 100,000 per year. This figure would appear to be too high when considering international data and would support the belief that there are inaccuracies in the method of coding for diabetes or age or both in the General Medical Services (Payments) Board data.

That this study provides a measure of ascertainment is valuable for future studies seeking to compare incidence rates and identify a secular trend.

4.7 Age of Onset

A number of studies show a bimodal distribution in the age of onset of diabetes with a peak in early childhood and a later maximum peak around the time of puberty. Sterkey et al(1978), Bloom et al (1975), Staines et al (1993), (Patterson et al, 1983). (Matsuura et al, 1998), mid-west Poland(Wielkopolska) (Rewers et al, 1987) and Hungary (Soltesz et al, 1990).

In this study a multimodal distribution is noted for Ireland. The peak age at diagnosis is at 8 and 10 years, with a smaller peak at 13-14 years and in early childhood at 3 and 6 years. This is younger than the age of onset reported in many other studies. Staines et al (1993), in the United Kingdom showed two peaks in age of onset at age 4-6 and age 10-15 years. Bloom et al (1975), showed a peak onset at approximately 11 years and a second peak at about five years. Patterson et al (1983), describe a peak age of onset at 11-12 years with a smaller peak at 3-4 years.

The overall mean age of onset was 8.7 years, standard deviation 3.7 years, and range of 13.8 years, from 1.09 to 14.9 years. Sterkey et al(1978), described the mean age of onset for both sexes combined at 8.2 years which is younger than found in this study.

The mean age of onset, noted in this study, for females at 8.2 years was slightly earlier than that in males at 9.2years but this failed to reach statistical significance ($p=0.106$). This is similar to the findings of other studies where girls are noted to have a slightly earlier (but not significant) disease onset than

boys (Sterkey et al 1978), (Staines et al 1993), (Metcalfe and Baum, 1991) (Reunanen et al, 1982 and Tuomilehto et al, 1991).

The number of cases diagnosed in girls generally rose through childhood to a small peak at 5 years, then declined and reached a maximum peak at 8 years and then declined with a second smaller peak at 14 years. The peak age of onset in Irish girls at 8 years is earlier than that reported in many other studies. The peak age of onset in girls described in other studies from Sweden, England, Scotland, the British Isles, Finland and Norway is older at 10 (Sterkey et al,1978 and Staines et al,1993), 11 (Dahlquist et al, 1982), and 12 years (Patterson et al, 1983, Metcalfe and Baum, 1991, Reunanen et al, 1982 and Joner et al, 1981).

The age of onset for males again showed a multimodal distribution. In boys the peak onset was at ages 9-10 and 13-14 years, with smaller peaks at ages 3 and 6 years. This is similar to the findings of Staines et al (1993), showed two peaks in age of onset in this population at age 4-6 and age 10-15 years in Yorkshire. Sterky et al (1978), described a peak incidence in boys at 7 and 13 years. A number of other studies show an older age of peak onset for boys, in Scotland a bimodal distribution was reported with a peak for boys at 11 years and another smaller peak at 3 years. In Sweden, Dahlquist et al (1982), showed a bimodal distribution for boys with peak onset at age 4 and 13 for boys. Metcalfe and Baum, (1991) showed a later peak onset between 12 and 13 years (mean 12.6). In Finland, the mean annual incidence rose throughout childhood and peaked in boys at 14 years with an abrupt decline after these

respective ages (Reunanen et al, 1982 and Tuomilehto et al, 1991). A similar pattern in age distribution has been reported in Norwegian children, by Joner et al (1981), with rising values throughout childhood to a plateau at 12-14 years for boys.

The peak age at diagnosis for Irish boys and girls is earlier than that reported in other studies. This could be interpreted as a recent effect of an environmental triggering factor(s) initiating the disease process.

4.8 Age Clustering

In this study clustering of cases was not demonstrated by year of birth due to the small numbers involved. The most frequent months of birth in those who subsequently developed diabetes were July, December, June and October. There was no significant difference when analysed by month of birth. When analysed by month and year of birth the numbers were too small to demonstrate effects of clustering. The importance of clustering of cases according to time of birth is that it gives support to the hypothesis that early environmental exposures, either pre-natally or early in life, are associated with the subsequent development of diabetes. Clustering of cases has been demonstrated by place and time of birth in Sweden (Dahlquist et al, 1996) and the north of England (Law et al, 1997) and clustering in time demonstrated in Iceland (Helgasson and Jonasson, 1981).

4.9 Seasonality of Diabetes Onset

A seasonal trend has been well documented in the clinical onset of diabetes in a large number of studies, with the majority of cases diagnosed in the cooler months of the year, Autumn/Winter, and the lowest number in the warmer months, Spring/Summer (Adams, 1926), (Gamble and Taylor, 1969), (Joner and Sovik, 1981), (Dahlquist et al, 1982), (Bloom et al, 1975), (Metcalfe and Baum, 1991), (Rangasami et al, 1997), (Levy-Marchal et al, 1995). In this Irish study the majority of cases were diagnosed in autumn (45 cases or 32.1%). There were 35 cases (25%) in Winter, 32 cases (22.9%) in Summer and 28 cases (20%) diagnosed in Spring. Thus, 57.1% of cases were diagnosed in Autumn/Winter and 42.9% of cases in Spring/Summer.

A number of studies failed to show a seasonal effect in the youngest, 0-4.99 year age category (Bloom et al, 1975),(Staines et al, 1993), (Rangasami et al, 1997). In this study, in the age category 0-4.55 years, 48.2% of cases were diagnosed in Spring/Summer and 51.8% in Autumn/Winter. Analysis of 26 centres confirmed a seasonal effect in all age groups and it is postulated that the failure to demonstrate a seasonal effect in the youngest age group in many studies is due to small numbers when centres are considered individually (Levy-Marchal et al, 1995). In the 10-14.99 year age category, 42.6% of cases were diagnosed in Autumn with 20.4% in Spring, and 18.5% in Summer and Autumn. In the 5-9.99 year age category, 33.9% of cases were diagnosed in Winter, with 22% of cases diagnosed in each of the three remaining seasons.

The most frequent month of diagnosis was October in which 14.3% of cases were diagnosed. A number of other studies also found the peak number of cases were diagnosed in October (Gamble and Taylor, 1969), (Joner and Sovik, 1981). Sterky et al (1978), found a high frequency of new cases in January, that did reach statistical significance and a tendency to a smaller peak in September/October.

Assessment of seasonality in this study did not achieve statistical significance due to the small number of cases. However, there was a fitted peak in October with an amplitude of 24.4%. This is in keeping with data from the EURODIAB ACE study (Levy-Marchal et al, 1995) with 4 of the 16 centres describing a peak of similar amplitude.

4.10 Infant Diet

Questions relating to the infant diet were poorly answered. Health professionals answered the questionnaires and the researcher was not permitted to contact parents to preserve confidentiality. Data regarding infant diet was generally not recorded in the patient notes and not available to the health professional completing the questionnaire.

4.10.1 Method of Feeding by year birth

Information regarding breast-feeding was available on 22.1% of cases. The majority of cases were bottle-fed from birth (77.4%) and only 22.6% were breast

fed. This is slightly lower than the national breast-feeding rates at approximately 30%, see Appendix V (Perinatal Statistics, 1991 and Perinatal Statistics, 1993) The maximum number of cases breast fed in any one year, by year of birth, was 2 cases in 1988.

A number of studies have demonstrated a protective effect of breast-feeding or an adverse effect of the early introduction of cow's milk-based formula feeds (Borch-Johnson et al,1984)(Hypponen et al, 1999)(Verge et al, 1994). However, the protective effect of breast-feeding only tends to occur where exclusive breast-feeding is continued for greater than 3 months(Verge et al, 1994) (Gerstein et al, 1994) . Information was available on the duration of exclusive breast-feeding for 6 of the 7 breast-fed cases. The duration of exclusive breast-feeding, ranged from 3 weeks (2 cases) to 6 months (2 cases). A further two children were breast fed in infancy for one month and six weeks respectively. The mean duration of breast-feeding was 2.7 months. The duration of exclusive breast-feeding in this study is too short in all but 2 cases to demonstrate an effect. Ireland has very low rates of breast feeding initiation but also has a very short duration of breast-feeding, with only 12% of babies were breast-fed at the age of 4 months in 1990 (Department of Health, 1994). The pattern of breast-feeding in this study is similar to that in the general population.

4.10.2 Age of Introduction of Cow's Milk

Information was available regarding the age of introduction of full cow's milk in only 10% or 14 cases. The earliest age at which cow's milk was introduced was 6 months (3 cases). The mean age at which cow's milk was introduced was 11.8

months. In the majority of cases the introduction of cow's milk was delayed until approximately one year of age which is the recommendation (Report of the Working Group on the Weaning Diet of the Committee on Medical Aspects of Food Policy, 1994).

There is much conflicting evidence regarding the role of cow's milk and breast-feeding in the aetiology of type 1 diabetes. A large prospective randomised control study of early infant feeding is currently underway in Finland which may answer many of the questions raised to date.

4.10.3 Age of Introduction of Solids

The time at which solid foods were introduced ranged from 7 weeks to 7 months, the mean age was 4.3 months. Data is available on 17 cases or 21%. 35% of cases introduced solid foods to the diet before 4 months. The recommended time for the introduction of solid food to infants is not earlier than 4 months and before 6 months (Report of the Working Group on the Weaning Diet of the Committee on Medical Aspects of Food Policy, 1994).

4.10.4 The Age of Introduction of Fruit Juice and Sugar to the Diet

Fruit juices were introduced to the diet in 25% before the age of 4 months. Fruit juices are not required for nutrition in the absence of vitamin C deficiency but can be offered from 4 months, if desired(Report of the Working Group on the Weaning Diet of the Committee on Medical Aspects of Food Policy, 1994). Sugar was added to the diet from 3.5 to 18 months, and in the first year of life in

25%. The mean age of the addition of sugar was 9.4 months. Added sugar is not recommended in an infant's diet (Report of the Working Group on the Weaning Diet of the Committee on Medical Aspects of Food Policy, 1994). In one child sugar and fruit juices were never included in the diet.

The response to the dietary component of the questionnaire is disappointing. No useful conclusions can be drawn from such small returns. It does suggest, however, that the dietary behaviour of cases is not dissimilar from that of the general population of Irish children. To evaluate diet further a prospective case-control design with the use of food diaries, patient contact and regular review would be most informative.

4.11 Family History

The majority of cases did not have a family history of insulin-dependent diabetes. This is consistent with data from other studies where up to 80% of those with the disease will not have a positive family history (Bennett, 1985). In this study 65% of cases had no family history of insulin dependent diabetes in either a first or second degree relative.

A positive family history of insulin dependent diabetes in a 1st degree relative was present in 11.5%, with 88.4% of cases having no such family history. This is similar to that found by Bloom et al (1995), in their study of the British Isles where 11% had a positive family history in a first degree relative. In other studies the proportion of those with insulin-dependent diabetes in a first degree

relative has been variably reported as 8.9%(Metcalfe and Baum, 1992), 12.8% (Dahlquist et al, 1985), and 23% (Calnan and Peckham, 1977).

The 1st degree relative with insulin dependent diabetes was: a sibling in 6 cases (46.1%); the child's father in 5 cases (38.5%); and the mother in 2 cases (15.4%). 6.2% of cases had a parent with insulin-dependent diabetes which is less than that found in a study of Swedish children where 8.1% had an affected parent (Dahlquist et al, 1985). In twice as many cases the affected parent was the father. This was the case in Sweden also with the frequency of diabetes in father's being 5.7% compared to mother's at 2.4% (Dahlquist et al, 1985). Metcalfe and Baum (1992), similarly report almost double the frequency of insulin dependent diabetes in fathers at 3.5% than mothers at 1.9%. Previous studies have shown the risk of a child developing IDDM if the father is affected is 4-6% while this is halved if the mother is the affected parent, the risk being 2-3% (Jefferson et al, 1985).

There was no significant difference between those who had a positive family history of insulin dependent diabetes in a first degree relative and the age category at diagnosis ($p= 0.226$). Similarly, no association was found between the age of disease onset and presence of a positive family history in Swedish children (Dahlquist et al, 1985). In contrast, British children showed an earlier onset of diabetes in those with an affected father but not an affected mother (Metcalfe and Baum, 1992).

21 patients (15%) had a positive family history of insulin dependent diabetes in a 2nd degree relative. The relative with insulin dependent diabetes was: an uncle; an aunt; a cousin; a grandparent.

13.6% had a family history of type 2, non-insulin dependent diabetes. In 4 cases there was a family history of both type 1 and Type 2 diabetes. In 68% of those with a family history of type 2 diabetes a grandparent was affected, in 21% an uncle, in 5.3% an aunt and in 5.3% there was a family history of type 2 diabetes in both grandparents, an uncle and an aunt.

4.12 Birth Order

There is some evidence that there is an increased risk of diabetes among first-born children (Wager et al, 1983 and Ramachandran et al, 1993). Patterson et al (1994), found the increased risk to the first born only in Northern Ireland and not in Scotland. In this study, 38.8% of cases were first-born children and 30.6% second-born. There was no significant difference in the number that were first or second born (P=0.362). This is in keeping with other studies that have failed to demonstrate an increased risk in first born children (Bock et al, 1994 and McKinney et al, 1999). The hypothesis for increased risk to first-born children relates to the hygiene hypothesis, that first-born children are in effective isolation from infection in early life and so do not benefit from the proposed protective effect of early infection. Failure to demonstrate an increased risk to first-born alone does not refute this hypothesis as there are likely to be many other factors influencing exposure to infection in early life.

4.13 Family Size

The number of occupants in the home has been considered as a potential risk factor in the development of diabetes. In this study the mean number of occupants in the home was 4.9, this is slightly above the national average of 4.4. The number of occupants ranged from 3 to 9. 32.7% of cases had 4 occupants in the home, 30.7% had 5 occupants and 25% of cases had 6 or more occupants in the home. Patterson et al (1994), found 19.8% of cases had 6 or more occupants compared with 23.6% of controls showing that 6 or more occupants in the home was associated with a slight but not significant reduction in diabetes. Other studies, however, have shown an increased risk of diabetes when living in larger groups (Siemiatycki et al, 1989 and Lawler-Heavner et al, 1991). There was a significant association between the age category at diagnosis and the number of occupants in the home ($p= 0.009$), those children diagnosed in the younger age categories tended to have fewer occupants in the home.

4.14 Number of Siblings

The number of siblings varied from none to six. 61.6% had 1 or 2 siblings. This would be consistent with the general population. Blom et al (1989), showed no difference in the number of siblings between cases and controls in Sweden. The number of siblings is likely to be highly associated with the number of persons living in a single house. A case control study is required to fully evaluate the effect of the number of household occupants and the number of siblings on the risk of diabetes development.

4.15 Presenting Clinical History

The most frequently reported clinical symptoms were polyuria and polydipsia in 93.7%, a further 2.1% reported polyuria alone. Only 2.9% reported no polyuria or polydipsia. The next most frequent symptom was weight loss, reported by 41% followed by lethargy in 14.3%. Polyuria, polydipsia and weight loss were similarly the commonest symptoms noted in 73% of those under 5 years and 81% aged 5-10 by Jefferson et al (1985). Polyphagia described by most authors as one of the main presenting symptoms of diabetes in children (Becker and Weber, 1995) was only reported in 1.4% of cases. Eneuresis in a previously toilet trained child is a recognised symptom but was found in this study as commonly as weight loss in 14.3%, nocturia was also common at 5%.

Other symptoms reported included, vomiting (5%), anorexia (2.1%), abdominal pain (2.1%), recurrent infections(2.1%), vulval pruritus or candidiasis(2.1%), increased appetite(1.4%), constipation (1.4%), asymptomatic or incidental diagnosis (1.4%), and headache, "strong smell from the nappies", family blood glucose check, generalised pruritus all reported by 0.7%.

4.15.1 Presenting Symptoms by Age Category

Polyuria and polydipsia are the most frequent symptoms at all ages, followed by weight loss. In the younger age categories eneuresis is also an important

symptom, occurring in 18.5% of those aged 0 – 4.99 years and 23.7% of those aged 5-10.99 years. Vomiting was the presenting symptom in 14.8% of the youngest children. In those aged 5-9.99 years, lethargy became an important symptom described in 16.9% of cases but only in 3.7% of those under 5. In the 10-14.99 year age category, polyuria and polydipsia (74.1%), weight loss (46.3%) and lethargy (16.7%) were the most frequently reported symptoms. A number of other symptoms were recorded in low frequency for each age category, all of which are well recognised in the literature.

4.15.2 Diabetic Ketoacidosis at Presentation

The definition of diabetic ketoacidosis used in this study was: blood glucose > 15 mmol, urinary ketones +2, pH < 7.2, HCO_3^- < 15 mmol and clinical symptoms which would represent moderate to severe diabetic ketoacidosis. 18.6% were in DKA at presentation, 50% of cases were not in DKA and a further 6% were treated as DKA but did not fulfil the above criteria. Data was not available on the remaining 35 cases (25%).

The reported frequency of presentation in diabetic ketoacidosis (DKA) is variable ranging and has been described in up to 30% at presentation (Becker and Weber, 1995). In the Oxford region, Pinkney et al (1994) found 16% of those diagnosed before age 21 were in severe diabetic ketoacidosis at presentation,(pH <7.10 or plasma bicarbonate < 10mmol/l), and 10% had mild to moderate diabetic ketoacidosis at presentation, (pH 7.10- 7.35 or plasma bicarbonate 10-21mmol/l). In the study by Pinkney et al (1994), 26% presented with moderate

to severe diabetic ketoacidosis which is similar to the finding in this study where the overall rate of presentation in diabetic ketoacidosis was 24.6%, when those who were treated as having DKA but did not fulfil the criteria (mild DKA) are included. A further 97 patients studied in 1990 found 26% to have diabetic ketoacidosis at presentation (Pinkney et al, 1994).

In those aged 0 – 4.99 years, 6 cases (25%) were in DKA at presentation and 16 cases (66.7%) were not. In those aged 5.99 – 10 years, 27.3% were in DKA at presentation and 63.6% were confirmed not to have DKA at presentation. In those aged 10 – 14.99 years, 21.1% were in DKA at presentation and 68.4% were confirmed not to have DKA at presentation.

There was no significant association between the age category at diagnosis and presentation in diabetic ketoacidosis (p=0.949). This is at variance with what has been observed in most other studies (Komulainen et al, 1999) (Pinkney et al, 1994) where the incidence of diabetic ketoacidosis at presentation was found to be highest in the youngest age group and become less frequent with increasing age. Increased severity of diabetic ketoacidosis has also been described in the younger age group (Komulainen et al, 1999) (Pinkney et al, 1994).

4.15.3 Duration of Symptoms

The majority of children and adolescents in this study had an abrupt clinical onset of diabetes with symptoms present for 2 weeks prior to diagnosis. This is

consistent with the findings from other studies, which describe a duration of symptoms of 2-3 weeks in most cases (Becker and Weber, 1995). However, there was a wide range of symptom duration from a few days up to 6 months, this has also been reported elsewhere (Becker and Weber, 1995).

The duration of symptoms was shortest in the youngest age category (p=0.022). The duration of symptoms increased with increasing age. The inter-quartile range for the age groups 0-4.99; 5-9.99; and 10-14.99 years was 10.5, 14 and 24.3 days respectively. Jefferson et al (1985) also found the duration of symptoms tends to be shorter in younger children. In their study 30% of children under 5 had a history of symptoms of less than 2 weeks compared to 12% of those aged 5-10years.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 CONCLUSIONS

Insulin-dependent diabetes mellitus is an important chronic disease with its peak incidence in the childhood and adolescent years. It is a disease associated with significant morbidity and premature mortality. Recent studies have proven that optimising medical management of this condition reduces the risk of long-term sequalae, thereby maximising health outcomes for those affected. Appropriate medical intervention increases both quantity and quality of life for these patients. The importance of this disease has been recognised by the World Health Organisation who deem information regarding the incidence of diabetes to be a basic national healthcare indicator. The planning and provision of appropriate services for those with diabetes depends on the availability of reliable data regarding the frequency of the disease in the population. To date no such information was available for the Irish population.

This study was performed to establish a national incidence rate of diabetes in those aged under 15 years and to define characteristics of the disease in the Irish population. It was hoped that this data would enable informed service planning for those with diabetes. This study has been greeted with enthusiasm by the health policy planners in the Department of Health and Children who are in the process of preparing a national strategy for diabetes.

In two previous studies of the British Isles that included Irish data, Ireland has been shown to have a low rate of type 1 (insulin-dependent) diabetes and one of

the lower rates of diabetes in Europe. However, this study shows that Ireland has a high incidence of diabetes in those aged under 15 years. The crude incidence rate of type 1 diabetes under the age of 15 was at least 16.6(13.7-19.2) per 100,000 per year and the standardised rate is 16.3 (14.2-18.5) per 100,000 per year. The incidence in Ireland is comparable with other areas of the British Isles. Indeed in Europe, only 23% of centres have a standardised incidence of diabetes above 15.0 per 100,000 per year, placing Ireland in the upper range of disease incidence. It is important that we are now recognised to have a moderately high incidence of this disease for allocation of adequate health care resources and service provision. Allocation of healthcare resources to this important disease is appropriate, as optimising medical treatment has been proven to influence health outcomes.

In keeping with other high incidence countries this Irish study shows a slight overall male predominance. Diabetes was diagnosed most frequently in those aged 5-9.99 years which is a younger age of onset than found in the rest of Europe at 10-14.99 years. We found significantly lower incidence rates in the youngest, 0-4.99 year, age category. The peak age at diagnosis in Irish children is younger, at 8 and 10 years, with a smaller peak at 13-14 years and in early childhood at 3 and 6 years. The mean age of onset is 8.7 years and slightly younger in girls compared with boys. We were unable to demonstrate clustering by month or year of birth.

A seasonal trend in the diagnosis of diabetes has been recorded throughout Europe in all age categories. We were unable to confirm statistically significant

seasonality at diagnosis due to small numbers. However, we did confirm a fitted peak of diagnoses in October with an amplitude of 24.4%, which is comparable with other centres.

The number of infants who were breast-fed in this study was low, in keeping with the trend in the general population. Similarly, the duration of exclusive breast-feeding is also short; too short to demonstrate any postulated protective effect which breast-feeding may have on the development of diabetes. There was variation in the age of introduction of cow's milk, solid foods, fruit juices and sugar to the diet. However, the majority introduced these foods at the recommended time. No useful conclusions can be drawn from these dietary practices as dietary information was limited to only 10% of cases.

The majority of Irish children with type 1 (insulin-dependent) diabetes do not have a family history of the disease in either a 1st degree (88%) or 2nd degree (85%) relative. We found in those children with an affected parent, this was twice as likely to be the father as the mother. Those children with a positive family history did not have an earlier onset of disease. There was no significant difference in the number of children who were first or second born in this study. The mean number of household occupants was 4.9 and two-thirds of the children had 1 or 2 siblings, which is consistent with national statistics.

Irish children present with the classical symptoms of diabetes, namely: polyuria, polydipsia, weight loss and lethargy. Polyphagia was not an important symptom in this group. Secondary eneuresis was a very important presenting symptom in

those aged under 10 years, as was vomiting in those under 5. Lethargy and weight loss became increasingly common symptoms in the older age groups. We found 18.6% were in moderate to severe diabetic ketoacidosis at presentation. There was no association between the age category at diagnosis and presentation in diabetic ketoacidosis.

The majority of children and adolescents in this study had an abrupt clinical onset of diabetes with symptoms present for only 2 weeks prior to diagnosis. There was, however, a wide range of symptom duration from a few days up to 6 months. The duration of symptoms was shortest in the youngest age category and increased with increasing age.

In this study, we have documented a high incidence rate for type 1 (insulin-dependent) mellitus in Irish children and adolescents under the age of 15 years. We have documented some characteristics of this patient group. We hope that this study will provide a basis for further research in this area.

5.2 RECOMMENDATIONS

We recommend that policy makers consider Ireland a high incidence country in future resource allocation and strategic planning decisions relating to diabetes.

A diabetes register should be established in Ireland to monitor the incidence of this very important disease and to establish if a secular trend is present in the Irish population, as has been documented throughout Europe. A register would enable accurate and timely measurement of disease frequency for healthcare provision and epidemiological study. Information available from such a register would enable the testing of hypotheses regarding aeitiology in this population. Ireland is still a relatively homogenous population, which would confer great advantage in epidemiological studies.

A further benefit is that a diabetes register allows rapid identification of those at increased risk of those developing the disease, namely siblings. These families may wish to avail of some of the primary preventative strategies to avoid diabetes development in the predisposed individual. These preventative strategies are currently the subject of wide international review and potential therapeutic options should be soon available. A register would also allow the care and management of those with diabetes be audited more objectively.

The support that we have received in this study from paediatricians, endocrinologists, physicians and diabetes nurse specialists would suggest that healthcare professionals would welcome and support such a disease register.

Further research is required to further define the characteristics of type 1 (insulin-dependent) diabetes in the Irish population. Such future studies could include a case-control study to evaluate perinatal events and family characteristics in diabetes, a prospective birth cohort study and a study of disease prevalence.

The importance of epidemiological studies in diabetes lies in the belief that they may help elucidate the aetiology of this important chronic condition.

CHAPTER SIX

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6. REFERENCES

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APPENDICES

APPENDIX I

Sample letter to Paediatricians

Dear Dr. ,

Re: **National Incidence Study of Insulin Dependent Diabetes Mellitus**

As a follow up to the Irish Paediatric Surveillance Unit National Study of Insulin Dependent Diabetes of Childhood we are putting together the study data and would gratefully appreciate your help. The aim of the study is to establish an incidence rate for diabetes in Ireland, looking at particular features such as the age of diagnosis, the season and the method of presentation of new diabetics.

I would gratefully appreciate your help in this study. Previous studies have suggested that the incidence of childhood diabetes in Ireland is significantly lower than elsewhere and we feel that this needs further clarification.

I would be grateful if you could clarify for me if any children, under the age of 18, presented to you for the first time with insulin dependent diabetes between **January 1st and December 31st 1997.** If so, would you be willing to complete the enclosed questionnaire on these children and return it to me. If due to time constraint you are unable to complete the enclosed questionnaire, would you grant me permission to access the patients charts in your institution so that the necessary data may be gathered. If you require any additional questionnaires please let me know. If no children presented to you in this time frame would you please return the enclosed slip marking no new cases seen.

I should be most grateful for your help and support with this study.

Yours sincerely,

Dr. Edna Roche
Lecturer in Paediatrics

Sample letter to Adult Physicians

Re: **National Incidence Study of**
Insulin Dependent Diabetes Mellitus

Dear Colleague,

I am currently attempting to establish an incidence rate for insulin dependent diabetes mellitus in Ireland and would greatly appreciate your help. This work is being undertaken as part of my M.D. research.

International studies have shown the incidence to have wide geographical variation and many countries have documented a significant increase in incidence recently. As you know no reliable data currently exists regarding the incidence in Ireland. Many of those with newly diagnosed insulin dependent diabetes will be young children and so present to paediatric centres. However, older children especially adolescents may make their first presentation to adult services. Were the survey solely restricted to the paediatric centres there would be a significant underestimation of the incidence.

I would be very grateful if you would let me know of any **new cases of insulin dependent diabetes under the age of 18** that have presented to you **between January 1st 1997 and December 31st 1997** on the sheet provided. If you have not seen any new cases in this period please return the sheet marking **"no cases seen"**.

I appreciate your support and look forward to your reply.

Yours sincerely,

Dr. Edna Roche
Lecturer in Paediatrics

National Incidence Study of Insulin Dependent Diabetes Mellitus

Case Definition: **Newly diagnosed Insulin dependent Diabetes**
Age: Birth *to* 17.9 years

Study Period: January 1st – December 31st 1997

New Cases Seen Jan 1997 – Dec 1997: **No** **Yes**
(circle as appropriate, if yes please give details below)

Replying Centre:

Name	Medical Record Number	Sex (M/F) *Circle as appropriate*	Date of Birth	Date of Diagnosis
		M F		
		M F		
		M F		
		M F		
		M F		
		M F		

Thank you for your assistance

Please return completed form(s) in the envelope provided to:

Dr. Edna Roche
Department of Paediatrics
The Adelaide and Meath Hospital incorporating the National Children's Hospital
Tallaght
Dublin 24

Please return this form even if no new cases of diabetes were seen by you in the selected time period

National Incidence Study of Insulin Dependent Diabetes

Aim: **to establish a national incidence rate for insulin dependent diabetes**

Time Period: **January 1st to December 31st 1997**

Age of Onset: **Birth to 18 years**

Number of New Cases Seen 1997:

[Please state if no cases seen]

Please return completed form(s) in the envelope provided to:

Dr. Edna Roche
Lecturer in Paediatrics
Department of Paediatrics
The Adelaide and Meath Hospital incorporating the National Children's Hospital
Tallaght
Dublin 24

APPENDIX II

National Incidence Study of Childhood Onset Insulin Dependent Diabetes

Identifying Data

Case Initials: _____ Chart Number: _____
Replying Centre: _____

General Patient Data

Date of birth: _____ Age (at diagnosis): _____

Sex: Male ☐ Female ☐

Number of occupants in home: _____
Birth order: _____
Number of Siblings: _____

Nutrition:

Was the infant breast fed? Yes ☐ No ☐
What was the duration of exclusive breast feeding? _____

Was the infant exclusively bottle fed? Yes ☐ No ☐
What was the age at introduction of cow's milk? _____

What was the age at introduction of solids? _____
What age was sugar added to the diet? _____

What age were fruit juices introduced? _____

Diagnosis:

Date of diagnosis: _____ **Season:**_____

Presenting complaint (please circle)

Diabetic Ketoacidosis Yes No
(DKA - blood glucose >15mmol, urinary ketones +2, pH<7.2, HCO3- <15mmol/L & clinical symptoms)
Polyuria/Polydipsia Yes No
Weight Loss Yes No
Other, please specify _____

Duration of presenting symptoms: _____

Family History of Diabetes:

		Yes	No	IDDM	NIDDM
In a	sibling	___	___	___	___
	twin	___	___	___	___
	mother	___	___	___	___
	father	___	___	___	___
	grandparent	___	___	___	___
	uncle	___	___	___	___
	aunt	___	___	___	___
	1st cousin	___	___	___	___

If more than one sibling has diabetes please state the number: _____

Associated Diseases:

Are any other significant associated diseases present in this child, e.g. Cystic Fibrosis or endocrinopathies (eg Adison, thyroiditis, Down Syndrome). Yes ☐ No ☐

If Yes, please state the diagnosis. _____

When was the primary disease diagnosed? _____

Therapy:

Was Insulin therapy required in this child? Yes ☐ No ☐

If no, please state the treatment given. _____

Thank you for your co-operation.

Please return the completed form (s) in the envelope provided to:

Dr. Edna Roche,
Department of Diabetes and Endocrinology
NCH
The Adelaide and Meath Hospital
incorporating The National Children's Hospital
Tallaght,
Dublin 24.

APPENDIX III

APPENDIX III

Irish Paediatric Surveillance Unit (I.P.S.U.) Response Rates (1997)

Month	% Response
January	89
February	88
March	92
April	90
May	90
June	85
July	86
August	86
September	88
October	89
November	81
December	81

APPENDIX IV

APPENDIX IV

Population data

Persons, males and females classified by single year of age

Age last birthday	Population			Population at or under this age		
Under 1 year	Persons	Males	Females	Persons	Males	Females
1 year	48,854	25,231	23,623	48,854	25,231	23,623
2 years	48,574	24,963	23,611	97,428	50,194	47,234
3 years	50,563	26,005	24,558	197,002	101,444	95,558
4 years	53,392	27,296	26,096	250,394	128,740	121,654
5 years	55,163	28,501	26,662	305,557	157,241	148,316
6 years	55,193	28,271	26,922	360,750	185,512	175,238
7 years	54,948	28,190	26,758	415,698	213,702	201,996
8 years	57,311	29,196	28,115	473,009	242,898	230,111
9 years	60,328	31,177	29,151	533,337	274,075	259,262
10 years	61,418	31,476	29,942	594,755	305,551	289,204
11 years	62,310	32,124	30,186	657,065	337,675	319,390
12 years	64,687	33,186	31,501	721,752	370,861	350,891
13 years	67,918	34,820	33,098	789,670	405,681	388,989
14 years	69,754	35,771	33,983	859,424	441,452	417,972
15 years	71,732	36,884	34,848	931,156	478,336	452,820

Table constructed with data from Table 5 Census 1996, Volume 2, Central Statistics Office

CENSUS AND INTERCENSAL ESTIMATES OF POPULATION

Estimated population classified by Sex and Age Group

Sex and Age Group	Persons in April of each year		
	1996[1]	1997[2]	1998[2]
Persons	000		
0 – 4 years	250.4	250.0	253.6
5 – 9 years	282.9	277.7	273.5
10 – 14 years	326.1	317.9	308.1
15 – 19 years	339.5	343.9	346.5

Sex and Age Group	Persons in April of each year		
	1996[1]	1997[2]	1998[2]
Males	000		
0 – 4 years	128.7	128.6	130.8
5 – 9 years	145.3	142.1	140.1
10 – 14 years	167.4	163.3	157.9
15 – 19 years	174.0	176.4	177.3

Sex and Age Group	Persons in April of each year		
	1996[1]	1997[2]	1998[2]
Females	000		
0 – 4 years	121.7	121.3	122.9
5 – 9 years	137.6	135.6	133.4
10 – 14 years	158.7	154.5	150.2
15 – 19 years	165.6	167.5	169.2

[1]Census of Population
[2]Preliminary figures

Table constructed with data from:

Population and Migration Estimates, April 1999, Central Statistics Office

APPENDIX V

APPENDIX V

IRISH BREAST-FEEDING STATISTICS

Percentage of mother's breast-feeding

Year	% breast-feeding
1985	34.1%
1986	33.9%
1987	33.2%
1988	32.3%
1989	32.8%
1990	31.7%
1991	31.9%
1992	33.9%
1993	33.9%

Table constructed with data from Perinatal Statistics, Ireland 1991 and Perinatal Statistics, Ireland 1993,
DEPARTMENT OF HEALTH AND CHILDREN

APPENDIX VI

DISEASES OF OTHER ENDOCRINE GLANDS (250-259)

250 Diabetes mellitus

Excludes: gestational diabetes (648.8)
hyperglycemia NOS (790.6)
neonatal diabetes mellitus (775.1)
nonclinical diabetes (790.2)
that complicating pregnancy, childbirth, or the puerperium (648.0)

The following fifth-digit subclassification is for use with category 250:

0 type II [non-insulin dependent type] [NIDDM type] [adult-onset type] or unspecified type, not stated as uncontrolled
1 type I [insulin dependent type] [IDDM] [juvenile type], not stated as uncontrolled
2 type II [non-insulin dependent type] [NIDDM type] [adult-onset type] or unspecified type, uncontrolled
3 type I [insulin dependent type] [IDDM] [juvenile type], uncontrolled

250.0 Diabetes mellitus without mention of complication
Diabetes mellitus without mention of complication or manifestation classifiable to 250.1-250.9
Diabetes (mellitus) NOS

250.1 Diabetes with ketoacidosis
Diabetic:
acidosis without mention of coma
ketosis without mention of coma

250.2 Diabetes with hyperosmolarity
Hyperosmolar (nonketotic) coma

250.3 Diabetes with other coma
Diabetic coma (with ketoacidosis)
Diabetic hypoglycemic coma
Insulin coma NOS

Excludes: diabetes with hyperosmolar coma (250.2)

250.4 Diabetes with renal manifestations

Use additional code to identify manifestation, as:
diabetic:
nephropathy NOS (583.81)
nephrosis (581.81)
intercapillary glomerulosclerosis (581.81)
Kimmelstiel-Wilson syndrome (581.81)

250.5 Diabetes with ophthalmic manifestations

Use additional code to identify manifestation, as:
diabetic:
blindness (369.00-369.9)
cataract (366.41)
glaucoma (365.44)
retinal edema (362.83)