GEOGRAPHIC VARIATIONS IN THE INCIDENCE OF DIABETES MELLITUS IN TAYSIDE, SCOTLAND

A thesis submitted to the University of St Andrews
for the Degree of Ph.D.

Matthew Cox

School of Geography & Geosciences,
University of St Andrews

November 2006

Declaration

i. I, Matthew Cox, hereby certify that this thesis, which is approximately 61,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous applications for a higher degree.

Date....9/3/07.. Signature of candidate.....

ii. I was admitted as a research student in October 2000 and as a candidate for the degree of Ph.D. in October 2001; the higher study for which this is a record was carried out in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date.....9/3/07 Signature of candidate..

iii. I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regualtions appropriate for the degree of Ph.D. in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date.....9/3/07 Signature of supervisor..

Unrestricted

In submitting this thesis to the University of St Andrews I understand that I am giving permission for it to be made available for use in accordance with regulations of the University Library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and abstract will be published, and that a copy of the work may be made and supplied to any bona fide library or research worker.

Date....9/3/07.. Signature of candidate....

TABLE OF CONTENTS

LIST OF TABLES ..... **iv**
LIST OF FIGURES ..... **vi**
ABSTRACT ..... **ix**
ACKNOWLEDGEMENTS ..... **xii**

CHAPTER 1 – INTRODUCTION TO THESIS **1**

CHAPTER 2 - DIABETES MELLITUS **5**
2.1 Introduction **5**
2.2 Type 1 diabetes mellitus **10**
2.2.1 Introduction to Type 1 diabetes 10
2.2.2 Gender and Type 1 diabetes 13
2.2.3 Age and Type 1 diabetes 13
2.2.4 Causes of Type 1 diabetes 16
2.3 Type 2 diabetes mellitus **37**
2.3.1 Introduction to Type 2 diabetes 37
2.3.2 Causes of Type 2 diabetes 40
2.4 Treating, monitoring and the complications of diabetes mellitus **59**
2.5 Conclusions **66**

CHAPTER 3 - GEOGRAPHY OF DIABETES MELLITUS **68**
3.1 Introduction **68**
3.2 Geography of Type 1 diabetes **68**
3.2.1 International variations in Type 1 diabetes incidence 69
3.2.2 Geographical variations in Type 1 diabetes incidence in the UK 76
3.2.3 Small area variations in the incidence of Type 1 diabetes 79
3.3 Geography of Type 2 diabetes **82**
3.3.1 International variations in diabetes prevalence 83
3.3.2 UK variations in diabetes prevalence 85
3.3.3 Small area variations in Type 2 diabetes prevalence 89
3.3.4 Conclusions 91

CHAPTER 4 – DEPRIVATION AND DIABETES MELLITUS IN TAYSIDE **95**
4.1 Tayside **95**
4.2 Deprivation **99**
4.2.1 Deprivation indices 101
4.2.2 Deprivation in Tayside 104
4.3 The Diabetes Audit and Research Tayside Scotland (DARTS) dataset **108**
4.4 The incidence of diabetes in Tayside **111**
4.5 Conclusions **116**

CHAPTER 5 – INTRODUCTION TO MANUSCRIPTS **121**

CHAPTER 6 – [MANUSCRIPT 1] DOES HEALTH-SELECTIVE MIGRATION FOLLOWING DIAGNOSIS STRENGTHEN THE RELATIONSHIP BETWEEN TYPE 2 DIABETES AND DEPRIVATION? **127**
6.1 Abstract **128**
6.2 Introduction **129**

6.3 Data and Methods 132
6.4 Results 135
6.5 Discussion 139
6.6 References 144
6.7 Tables & figures 147

CHAPTER 7 – [MANUSCRIPT 2] LOCALITY DEPRIVATION AND TYPE 2 DIABETES INCIDENCE IN TAYSIDE, SCOTLAND: A LOCAL TEST OF RELATIVE INEQUALITIES 159
7.1 Abstract 160
7.2 Introduction 162
7.3 Method 167
7.4 Results 170
7.5 Discussion 171
7.6 References 179
7.7 Tables & figures 183

CHAPTER 8 – [MANUSCRIPT 3] CHILDHOOD TYPE 1 DIABETES, POPULATION MIXING AND THE HYGIENE HYPOTHESIS 186
8.1 Abstract 187
8.2 Introduction 189
8.3 Methods 192
8.4 Results 195
8.5 Discussion 196
8.6 References 202
8.7 Tables & figures 207

CHAPTER 9 – [MANUSCRIPT 4] UPTAKE OF REAGENT STRIPS, DEPRIVATION AND ACCESS TO SERVICES 211
9.1 Abstract 212
9.2 Introduction 213
9.3 Data & Methods 217
9.4 Results 220
9.5 Discussion 222
9.6 Acknowledgements 226
9.7 References 227
9.8 Tables 230

CHAPTER 10 – DISCUSSION & CONCLUSIONS 232
10.1 Discussion of results 232
10.2 Limitations of the study 236
10.3 Conclusions 240
10.4 Future Work 240

REFERENCE LIST 243

LIST OF TABLES

Table 2.1 Estimated diagnosed Type 1 diabetes in the UK by age in 2004 (Diabetes UK, 2004) 16

Table 2.2 Viruses associated with Type 1 diabetes in humans and animals after Hyöty & Taylor (2002, p. 1354) and Jun & Yoon (2003, pp. 9-10). 26

Table 2.3 Risk factors associated with Type 2 diabetes. Variables shown in italics are not firmly established (after Dabelea & Hamman, 2004, p. 792) 43

Table 2.4 Common complications of diabetes mellitus (source Lundstrom, Mordes, & Rossini, 1998) 60

Table 3.1 Average annual age-standardised incidence of Type 2 diabetes (per 100,000) in nine British towns, 1977-1979. Taken from Barker, Gardner, & Power (1982, p.423). 89

Table 3.2 Adjusted odds ratios for Type 2 diabetes prevalence by Carstairs deprivation category in Tayside, January 1993 (taken from Evans, Newton, Ruta et al., 2000). 90

Table 6.1 Number and mean age (± standard deviation) of diagnosis of people with Type 2 diabetes in three groups within the cohort, by sex 147

Table 6.2 Number of people with Type 2 diabetes moving between deprivation quintiles for three groups by mobility status 148

Table 6.3 The ratios between the SIRs for deprivation quintiles 1 and 5 at diagnosis and at the end of study/time of death for the three groups by mobility status 149

Table 7.1 Type 2 diabetes incidence (univariate models) 183

Table 7.2 Type 2 diabetes incidence (multivariate model) 184

Table 8.1 Descriptive statistics for the continuous variables used in the analysis 207

Table 8.2 Type 1 diabetes among children, 0-14, by combined measures of population mixing 208

Table 8.3 Type 1 diabetes among children, 0-14 (univariate models) 209

Table 9.1 Number of persons with Type 2 diabetes by treatment and the type of glucose testing strips dispensed, Tayside, 1999. 230

Table 9.2 Multiple logistic regression models for the uptake of urine testing strips for persons with diet and oral tablet treated diabetes or blood testing strips for person with insulin treated diabetes 231

LIST OF FIGURES

Figure 2.1 Percentage prevalence of diabetes (all Types) from various studies in the UK (reported in Harvey, Craney, & Kelly, 2002) and estimations by Diabetes UK (Diabetes UK, 2004, 2005b). 8

Figure 2.2 Age of diagnosis for children in the National Paediatric Diabetes Audit (taken from Diabetes UK, 2002, p.11) 14

Figure 2.3 Type 1 diabetes incidence rate by age at diagnosis and sex. Solid line: male; dashed line: female. Solid line: male; dashed line: female. (Taken from Staines, Bodansky, Lilley et al., 1993). 15

Figure 2.4 Risk factors for Type 2 diabetes mellitus from a life course prospective (taken from Dabelea & Hamman, 2004, p.790). 41

Figure 2.5 Annual age-specific incidence rates of newly diagnosed Type 2 diabetes by sex in Poole 1996-8 (taken from Gatling, Guzder, Turnbull et al., 2001, p.110). . 45

Figure 2.6 Prevalence of diagnosed diabetes by ethnic group in England, 1999 (source Joint Health Surveys Unit, 2001). 47

Figure 2.7 The effects of excess calories and a sedentary lifestyle in leading to the development of obesity, insulin resistance, impaired glucose homeostasis and, Type 2 diabetes (Silink, Kida, & Rosenbloom, 2003 p.3). 53

Figure 2.8 Prevalence of non-insulin treated Type 2 diabetes by deprivation category, 1994-98, England & Wales (source Office for National Statistics, 2000). 56

Figure 3.1 Published incidence rates of Type 1 diabetes (cases per 100,000 population per year) in children aged 0-14 year old by country (taken from the International Diabetes Federation, 2003, p.118) 70

Figure 3.2 Trends in the incidence of Type 1 diabetes mellitus in European populations. 73

Figure 3.3 Trends in the incidence of Type 1 diabetes mellitus in Non-European populations. 74

Figure 3.4 Association between the increase in incidence and the level of incidence of Type 1 diabetes. 75

Figure 3.5 Age-standardised childhood Type 1 diabetes incidence rate per 100,000 children by Health Board in Scotland, 1984-2000 (Source: Scottish Study Group for the Care of Diabetes in the Young, published in Scottish Diabetes Survey Monitoring Group, 2004) 78

Figure 3.6 Childhood (0-14 years) Type 1 diabetes and population density in Yorkshire. (Taken from McKinney, Law, Bodansky et al., 1996). 81

Figure 3.7 Estimated prevalence of diabetes by country (taken from the International Diabetes Federation, 2003, p.26) 84

Figure 3.8 Age standardised diabetes prevalence for NHS Health Boards in Scotland, 2003. Orkney data from 2001, Western Isles data from 2002. (Taken from Scottish Diabetes Survey Monitoring Group, 2004, p.14)..... 88

Figure 4.1 NHS Scotland Health Boards in 2001. Tayside Health Board is labelled as '6'. (Created using boundaries from UK Borders). 96
Figure 4.2 Relief map of Tayside also showing roads and major settlements. Digital boundaries from UK Borders, Digital Elevation Model courtesy of Digimap, © Crown Copyright/database right 2006. An Ordnance Survey/(Datacentre) supplied service. 97

Figure 4.3 The variables which make up the Carstairs Deprivation Index (Carstairs & Morris, 1991) 103

Figure 4.4 Carstairs Deprivation Index 2001 for Scottish NHS Health Boards (created using boundaries from UK Borders and 2001 Census data). 106

Figure 4.5 Carstairs Deprivation Index 2001 for Tayside output areas (created using boundaries from UK Borders and deprivation data from 2001 Census)..... 107

Figure 4.6 Age/Sex standardised Type 1 diabetes incidence by CAS sector in Tayside for 1998-2001. The rate for the Tayside Health Board is shown on the right-hand end of the figure. (Data obtained from DARTS). 114

Figure 4.7 Age/Sex standardised Type 2 diabetes incidence by CAS sector in Tayside for 1998-2001. The rate for the Tayside Health Board is shown on the right-hand end of the figure. (Data obtained from DARTS). 115

Figure 4.8 Map of age/sex standardised rates for Type 1 diabetes incidence in Tayside by CAS sector, 1998-2001. (Created using boundaries from UK Borders and DARTS data)..... 118

Figure 4.9 Map of age/sex standardised rates for Type 2 diabetes incidence in Tayside by CAS sector, 1998-2001. (Created using boundaries from UK Borders and DARTS data)..... 119

Figure 4.10 Type 2 diabetes age/sex standardised incidence against Carstairs Deprivation Index for CAS sectors in Tayside, 1998-2001. (Created using DARTS data and deprivation data from the 2001). 120

Figure 6.1 Carstairs deprivation by CATT in Tayside, Scotland, 2001..... 150

Figure 6.2 Standardised Incidence Ratios for Type 2 diabetes by deprivation at diagnosis and the end of the study period in Tayside, Scotland: survivors (bars are 95% confidence intervals)..... 151

Figure 6.3 Standardised Incidence Ratios for Type 2 diabetes by deprivation at diagnosis and the end of the study period in Tayside, Scotland: surviving non-movers (bars are 95% confidence intervals). 152

Figure 6.4 Standardised Incidence Ratios for Type 2 diabetes by deprivation at diagnosis and the end of the study period in Tayside, Scotland: surviving movers (bars are 95% confidence intervals). 153

Figure 6.5 Standardised Incidence Ratios for people with Type 2 diabetes who died between 1996 and the end of the study period and deprivation in Tayside, Scotland: incidence and prevalence (bars are 95% confidence intervals). 154

Figure 6.6 Standardised Incidence Ratios for people with Type 2 diabetes who died between 1996 and the end of the study period and deprivation in Tayside, Scotland: incidence and prevalence of non-movers (bars are 95% confidence intervals). 155

Figure 6.7 Standardised Incidence Ratios for people with Type 2 diabetes who died between 1996 and the end of the study period and deprivation in Tayside, Scotland: incidence and prevalence of movers (bars are 95% confidence intervals). 156

Figure 6.8 Standardised Incidence Ratios for people with Type 2 diabetes who died before 1996 and deprivation in Tayside, Scotland: incidence and prevalence (bars are 95% confidence intervals). 157

Figure 6.9 Standardised Incidence Ratios for people with Type 2 diabetes who died before 1996 and deprivation in Tayside, Scotland: incidence and prevalence of movers (bars are 95% confidence intervals). 158

Figure 7.1 Carstairs deprivation by output areas in Tayside, Scotland, 2001 185

ABSTRACT

The incidence of diabetes is increasing both in the UK and worldwide. However, to date relatively little research has considered the social and geographical aspects of this condition. Via a portfolio of four research papers, this thesis analyzes geographical variations in Type 1 and Type 2 diabetes incidence in small areas of Tayside, Scotland. It considers how the deprivation characteristics of places are related to the incidence of diabetes, how health-selective mobility may influence this relationship, and whether patient self-monitoring is influenced by access to pharmaceutical services.

The first paper considers how health-selective residential migration may influence the relationship between diabetes and deprivation. The prevalence of Type 2 diabetes is known to be positively associated with socio-economic deprivation. However, health-selective migration following diagnosis may alter the association between diabetes and deprivation, perhaps suggesting a stronger relationship than existed at the time of diagnosis. A comparison of the deprivation quintiles of area of residence for a cohort of people with Type 2 diabetes at: a) time of diagnosis and b) 8-18 years later indeed shows that Type 2 diabetes incidence is significantly associated with deprivation and that this relationship strengthens over time. The primary reason for this is not, as might be expected, the health-selective 'downward' mobility of people with diabetes into the most deprived areas, although some do experience this process. Instead, the major reason for this effect is the health-selective immobility of those with diabetes in the more deprived areas. Those with Type 2 diabetes tend to remain in areas that become relatively more deprived over time.

The second paper considers how the 'relative deprivation context' may influence Type 2 diabetes. This paper contributes to the theoretical debate between material and psycho-social influences on health inequalities, by testing how the deprivation circumstances in areas surrounding a particular neighbourhood may influence diabetes, controlling for the deprivation circumstances of that neighbourhood. The results demonstrate that in Tayside areas surrounded by relatively less deprived areas had lower incidence of Type 2 diabetes than expected, and areas surrounded by more deprived areas had a higher incidence of Type 2 diabetes. The results lend credence to more materialist explanations of socio-spatial effects on health, such as the 'pull-up/push-down hypothesis'. They do not support a psycho-social interpretation of the effect of relative deprivation on diabetes incidence.

The third paper focuses on Type 1 diabetes. Similar to studies elsewhere, deprivation does not appear to influence the geographic variation of Type 1 diabetes in Tayside. According to the 'hygiene hypothesis' we might expect the incidence of Type 1 diabetes to be lower in areas where 'population mixing' (a proxy for the spread of pathogens) is low. Our results indeed demonstrate that population mixing is inversely related to childhood Type 1 diabetes incidence; areas with a low percentage of child in-migrants from a narrow set of origins have the highest incidence of childhood diabetes. These results appear to support the 'hygiene hypothesis' as areas that are relatively free of infections may leave children prone to Type 1 diabetes due to their lack of acquired immunity.

The final paper considers the factors that influence blood glucose self-monitoring. Self-monitoring is an important component of blood glucose management

programmes and can have a positive impact on the lives of people with diabetes. We considered whether geographical access to pharmacies was related to the cashing of prescription for blood and urine testing strips by people with Type 2 diabetes. The results show that those patients who are treated with diet interventions or oral hyperglycaemic agents (less advanced diabetes), are less likely to cash a prescription for urine testing strips the further away from the nearest pharmacy they live. However, people with more advanced diabetes, who require insulin treatment, cash in prescriptions for blood testing strips irrespective of the distance to the pharmacy. On the one hand, these are positive results as those with more advanced diabetes appear to be engaging in self-monitoring. On the other hand, those with less advanced diabetes seem less willing to engage in this behaviour and this may have significant implications for how their condition is handled. These results are also policy-relevant, given the recent debates within the Scottish Executive about the necessity/costs of keeping rural pharmacies open.

In combination, the novel results presented in this thesis highlight the importance of social processes in the production of the geographies of diabetes mellitus. They demonstrate that geography matters and that future strategies for reducing the 'diabetes epidemic' should take this into account.

ACKNOWLEDGEMENTS

My heartfelt thanks must firstly go to Prof Paul Boyle and Prof Peter Davey for giving me the opportunity to do this Ph.D. and for their excellent supervision, enthusiasm and encouragement on what has been a long and winding road.

From the School of Geography & Geosciences, St Andrews University, I must thank Dr Jamie Pearce (now of Canterbury University), Dr Zhiqiang Feng, Dr Daniel Exeter (now of Auckland University), Dr David Manley, Prof Robin Flowerdew, Mr Stuart Allison and Mr Colin Cameron for their invaluable knowledge and help down the years. I would also like to express my gratitude to the numerous people involved in my work from the various units of Ninewells Hospital and the University of Dundee: chief amongst them being Prof Andrew Morris, Dr Josie Evans, Mr Philip Thomson, and Mr Ritchie MacAlpine. In addition, I would also like to thank the many other people who have contributed to the DARTS collaboration from which most of the data used in this thesis was drawn.

Outside the project I would like to pay tribute to the fantastic group of people whose time has coincided with mine at St Andrews. Jamie & Pig, Nick & Beccy, Chrispy & Ruth, Lara & Chris, Emilie & Gav, Leon & Natalie - thank you for your friendship and proving the old cliché that 66% of St Andrews students meet their future partner at the University. Of course just as much thanks must also go to the singletons - Jojo, Beth, Mog, Maerkey & Goose, keep up the good work! Finally, and above all else, I would like to thank Alix Cage for her love and support, her chivvying, and for keeping me sane.

CHAPTER 1 – INTRODUCTION TO THESIS

Diabetes is a chronic health condition where the body is unable to produce insulin and properly break down sugar (glucose) in the blood. Glucose is the main source of chemical energy available from food and, as a consequence, diabetes commonly results in symptoms such as extreme tiredness and weight loss. More importantly, the rising concentrations of glucose in the blood stream typically results in increased urination and extreme dehydration which, when left untreated, can quickly result in death. In the long-term, diabetes is associated with a set of serious complications, such as blindness, kidney failure, cardiovascular disease and gangrene (leading to amputation), which reduce quality of life and are a major cause of premature death amongst people with diabetes (Roper, Bilous, Kelly, Unwin, & Connolly, 2001).

There are now an estimated 2 million people in the UK diagnosed with diabetes and perhaps another million who remain undiagnosed (Diabetes UK, 2005b). Over the last 40 years, UK studies of diabetes have shown that the prevalence of the condition has increased exponentially (Harvey, Craney, & Kelly, 2002) and this increase looks set to continue for the foreseeable future (Wild, Roglic, Green, Sicree, & King, 2004) in what has been dubbed the 'diabetes epidemic'. At present the treatment of diabetes and diabetic complications costs the NHS ~£10 million a day. This equates to 9% of the NHS budget and this figure is predicted to rise to 10% by 2011 (Diabetes UK, 2005a). Clearly the increasing incidence of diabetes is of great concern, both in terms of the effect it has on longevity and quality of life, and also upon wider societal impacts, such

as the ability of people with diabetes to work, the strain it places on healthcare resources and the cost to the national welfare system.

A wide literature has investigated the individual characteristics and behaviours of people who develop diabetes, and the role of gender, age, ethnicity, obesity and lack of physical exercise has been examined in the UK (e.g. UK Prospective Diabetes Study, 1988). However, few studies have explored how the characteristics of where one lives affect the probability of developing diabetes, i.e. the importance of 'place'. This thesis expands our understanding of the social causes of diabetes by considering geographic variations in the incidence of diabetes in small areas in Tayside for both childhood and adult diabetes.

This thesis consists of a portfolio of research papers submitted to international journals. Each manuscript utilises geographic data analysis techniques to offer novel insights either into the role of place in the aetiology of diabetes or how geographic access to services may impinge upon self-care by people with diabetes. The first manuscript (Chapter 6) assesses the relationship between Type 2 diabetes and deprivation. It then explores whether the deprivation gradient for Type 2 diabetes is influenced by health-selective migration. Thus, by following a cohort of people diagnosed with diabetes, we explore whether their subsequent geographical mobility results in them living in more or less socio-economically deprived areas following diagnosis. The results have important implications, particularly for studies which rely on prevalence rates.

Having demonstrated that Type 2 diabetes is associated with deprivation, the second manuscript (Chapter 7) considers whether 'relative deprivation context' also influences this outcome. By considering deprivation in both the residential area and the surrounding area, it is possible to test whether relative socio-economic circumstances influence diabetes. The results provide an interesting take on the recent debate about the role of psycho-social influences on health, particularly in relation to Wilkinson's theory of relative inequality (Wilkinson, 1996).

The third manuscript (Chapter 8) focuses on Type 1 diabetes which is more common in rural settings than might be expected. One interesting theory relates to the 'hygiene hypothesis', which suggests that children growing up in areas which are relatively free of infections may be prone to subsequent auto-immune diseases due to their lack of acquired immunity. We explore whether this is the case by considering the relationship between population mixing (used as a proxy for the spread of pathogens) and childhood Type 1 diabetes in small areas of Tayside. The results support this theory.

The fourth and final manuscript (Chapter 9) uses prescription data to consider whether geographic distance to the nearest pharmacy is related to whether a person with diabetes self-monitors their blood glucose. This is the only manuscript in the thesis which does not deal with diabetes as the outcome variable. The analysis demonstrates that for those with early or middle stage diabetes, who tend to rely on urine testing, distance to the nearest pharmacy is significantly related to prescription cashing. For those whose diabetes is at an advanced stage, requiring insulin treatment and blood glucose monitoring, there is no distance decay effect. This is the first study to date

which examines such access questions in relation to diabetes care and the results have policy-relevant implications, given recent debates within the Scottish Executive about the necessity to keep rural pharmacies open.

Of course, each of these manuscripts is designed to stand alone, and can be read in isolation from the rest of the thesis. However, the thesis also includes a substantial literature review, focusing on: the aetiology and risk factors of diabetes (Chapter 2); what is already known regarding the geography of the condition (Chapter 3); and an introduction to Tayside and the Diabetes Audit Research Tayside Scotland (DARTS) dataset, including some original analysis of the incidence of diabetes in Census Area Statistic (CAS) sectors, which provides a general background to the condition in the region (Chapter 4). Chapter 5 briefly appraises the research aims and methods in each of the manuscripts. Following the manuscripts, Chapter 10 provides a critical discussion of the results presented in the manuscripts, before drawing conclusions for the thesis as a whole and highlighting potential future research.

CHAPTER 2 - DIABETES MELLITUS

2.1 Introduction

Diabetes mellitus is a state of chronic hyperglycaemia (increased blood glucose), classically characterised by extreme tiredness, excessive thirst, increased urine volume, itching, regular episodes of thrush, blurred vision and weight loss. Indeed, the term diabetes was originally coined by Arataeus of Cappadocia, 2,000 years ago, to describe one of the more obvious symptoms of hyperglycaemia. In the Greek language, 'diabaínein' literally means "to run through" (Foster, 1992) making reference to the need for more frequent and more copious urination by people with diabetes. Arataeus described diabetes as 'a melting down of the flesh and limbs into urine' reflecting the weight loss and excess passing of urine that occurs in acute undiagnosed diabetes (ABPI, 2005). Thomas Willis (1621-1675) added the term 'mellitus', which is Latin for 'honey sweet', because some excess glucose is lost to the sufferer's urine, which physicians of the time often tasted for diagnostic purposes.

The unifying feature in all cases of diabetes is the defective secretion of insulin and/or the decreased sensitivity of cells to the action of insulin. Insulin is produced by the β-cells, which reside in the islets of Langerhans in the pancreas, and is the key hormone involved in the storage and controlled release of chemical energy available from food. This chemical energy takes the form of circulating blood glucose. Following meals,

blood glucose concentrations rise and this is accompanied by an associated peak in insulin production. The effect of insulin is to lower the threshold for glucose to enter cells of the body where it can be stored, usually in the liver, as glycogen. When insulin levels decrease in-between meals or in response to exercise, another hormone, glucagon, is produced, initiating the process of gluconeogenesis converting glycogen back to glucose to use as an energy source. In a healthy person, blood glucose levels are normally regulated to 3.5 - 8.0 mmol L^{-1} (Kumar & Clark, 1998) predominantly by the action of insulin in association with glucagon, and other hormones such as adrenalin. However in people with diabetes, the ability to produce insulin, or the sensitivity of the body's cells to insulin, has become impaired. The cells of the body cannot take up the glucose available in the blood and this causes blood glucose concentrations to rise.

Once blood glucose levels exceed the renal threshold (i.e. the level at which a substance is excreted by the kidneys) at around 9.0 - 10.0 mmol L^{-1}, a person will start to dehydrate as water is used to carry some of the excess glucose out of the body in urine. The person will begin to display the symptoms of associated with hyperglycaemia (i.e. they become 'symptomatic'). If blood glucose concentration rises in excess of 15.0 mmol L^{-1} diabetic ketoacidosis may occur where, unable to use circulating glucose, the liver reacts as though the body is starving by producing more glucose (by breaking down proteins) and massive quantities of ketone bodies (by breaking down fatty acids). Ketone bodies are acidic and so have the effect of lowering the pH value of the blood. At the same time, the glucose and ketone bodies in the bloodstream increase the osmolal load of the blood leading to extreme dehydration as water is drawn out of cells.

Dehydration further increases the osmolality of the blood and more water is drawn out of cells. If left untreated the dehydration caused by this cycle will result in a coma or death.

In the long-term, hyperglycaemia also results in micro- and macro- vascular damage, and thus poorly controlled diabetes is often associated with a set of common complications such as progressive eye, kidney, nerve and artery damage (Bell & Hockaday, 1996). Therefore following a diagnosis of diabetes, the emphasis of medical treatment is to keep blood glucose as close to normal levels as possible (normoglycaemia). If tight control of blood glucose levels can be achieved using the various therapies available for the treatment of diabetes (see section 2.4), the appearance of short-term symptoms and the long-term risk of complications can be significantly reduced (DCCT Research Group, 1993; UK Prospective Diabetes Study Group, 1998b).

In September 2005, Diabetes UK, estimated that there were over 2 million people in the UK (3.3% of the UK population) diagnosed with diabetes mellitus, whilst up to a million more people may have undiagnosed diabetes (Diabetes UK, 2004, 2005b). Over the last 40 years, studies of diabetes conducted in the UK have shown that the prevalence of the condition has increased exponentially. This is highlighted in Figure 2.1 where the percentage prevalence of diagnosed diabetes has increased from 0.6% in 1962 (based on a study in Birmingham, reported in Harvey, Craney, & Kelly, 2002) to 3.3% of the population in 2005 (based on UK estimates reported in Diabetes UK, 2005). Furthermore, based on reported current trends (Karvonen, Tuomilehto,

Libman, & LaPorte, 1993; Onkamo, Vaananen, Karvonen, & Tuomilehto, 1999; Passa, 2002) and a number of predictions (Amos, McCarty, & Zimmet, 1997; International Diabetes Federation, 2003; Wild, Roglic, Green et al., 2004) diabetes prevalence looks set to keep rising, both in the UK and worldwide. An ageing population, combined with increased obesity and lack of physical exercise (which are known to be key risk factors; UK Prospective Diabetes Study Group, 1988) look set to drive what the media have dubbed the 'diabetes epidemic' (for example see Revil, 2003) both in the UK and abroad.

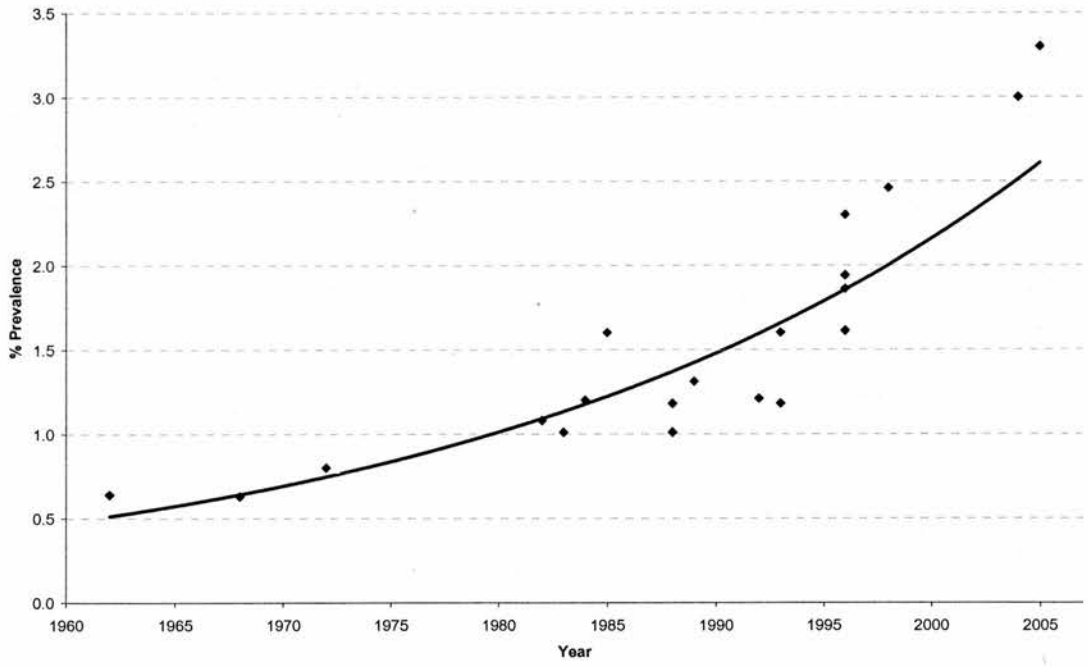


Figure 2.1 Percentage prevalence of diabetes (all Types) from various studies in the UK (reported in Harvey, Craney, & Kelly, 2002) and estimations by Diabetes UK (Diabetes UK, 2004, 2005b).

In the UK there are two main categories or 'Types' of diabetes: Type 1 and Type 2. These Types can be considered as patterns of pancreatic failure rather than as disease processes. In any given case of diabetes there are any number of disease processes (known or unknown), which may either act individually or in multiples to trigger the on-set of the condition. However the two Types of diabetes are used to categorise each case depending on clinical presentation and the broad aetiology of the disease processes at work. Type 1 diabetes most often results from autoimmune processes, in which the person's own immune system is responsible for the destruction of pancreatic β-cells, leading to the inability to produce native insulin. The disease mechanisms in Type 2 diabetes are less clearly understood but are most easily differentiated from Type 1 by the lack of autoimmune activity, and the age and weight of the sufferer. Type 2 is also usually characterised by a less pronounced decline in insulin production and/or the loss of sensitivity to the action of insulin by peripheral tissues (termed 'insulin resistance').

There are substantial differences between Type 1 and Type 2 diabetes. The remainder of this chapter addresses each Type separately, and provides a review of their aetiology. Aetiological differences, in association with social and cultural phenomena, result in distinctly different geographies of the diabetes Types and this will be addressed in Chapter 3.

2.2 Type 1 diabetes mellitus

2.2.1 Introduction to Type 1 diabetes

There are thought to be around 18,000 people in Scotland and 237,000 people in the UK as a whole with Type 1 diabetes (Diabetes UK, 2004). This equates to ~0.40% of the UK population and Type 1 diabetes accounts for ~12.5% of all people with diabetes. Although the growing debate surrounding the 'diabetes epidemic' is primarily concerned with Type 2 diabetes and its causes, it is interesting to note that despite the smaller numbers involved the incidence of Type 1 diabetes in the UK, it is thought to have doubled every decade since 1945 (Barnett, 1998).

Type 1 diabetes tends to result in the near total destruction of all β-cells, resulting in the person being totally dependent on injections of exogenous insulin. For this reason Type 1 diabetes is often referred to in older texts and studies as 'Insulin Dependant Diabetes Mellitus' (IDDM). However, although nearly all people with Type 1 diabetes are insulin dependent, some 13.6% (McAlpine & Cunningham, 2004) of people with Type 2 diabetes in Tayside (Scotland) also have the severity of condition to require insulin treatment. Although it may be easier to categorise patients on the basis of their treatment, this more simplistic categorisation may combine populations with very different disease processes, particularly as more young people are developing Type 2

diabetes. Therefore most modern studies, and all the original work presented in this thesis, use the Type 1/Type 2 categorisation.

Following the drastic loss of insulin-producing capacity associated with Type 1 diabetes, a person will soon exhibit clear symptoms of hyperglycaemia and is much more prone to developing potentially fatal diabetic ketoacidosis than a person with Type 2 diabetes. They will therefore normally either present themselves to medical physicians or enter hospitals as an emergency admission, and it is unlikely that their diabetes will remain undiagnosed for any length of time. As people with Type 1 diabetes are often symptomatic (i.e. experiencing the symptoms of hyperglycaemia) the diagnosis of diabetes is relatively straightforward.

In the UK procedures for the diagnosis of diabetes comply with guidelines published by the World Health Organisation (WHO, 1999). In a symptomatic person a diagnosis of diabetes can be established simply if they have a non-fasting blood glucose level in whole veinous blood (from a vein) of 10.0 mmol L^{-1} or more. If the blood glucose level is between 4.4 - 10.0 mmol L^{-1} (veinous blood) or 4.4 - 11.1 mmol L^{-1} (capillary blood, e.g. from the end of the finger) then the diagnosis is more problematic and requires an oral glucose tolerance test (OGTT). The OGTT is normally carried out after 3 days or more of unrestricted diet and usual physical activity. After an evening meal of 30-50g of carbohydrate the person fasts overnight. The following morning a blood test is taken and the person then consumes a drink containing 75g of glucose. Two hours after the drink another blood sample is taken. If the person has a blood glucose level after the

overnight fast of 6.1 mmol L^{-1} or more, or if the blood glucose level is 10.0 mmol L^{-1} or more 2 hours after the glucose drink, then the person is diagnosed as having diabetes.

As discussed above, following a diagnosis of diabetes, Type 1 is usually differentiated from Type 2 diabetes by the presence or absence of an autoimmune reaction to the insulin-producing pancreatic β-cells. This reaction can normally be detected by the presence of antibodies to islet cells, and/or antibodies to insulin, and/or antibodies to glutamic acid decarboxylase (GAD, which is an enzyme found in the β-cell islets). However, these antibodies are only present in 85-90% of individuals with Type 1 diabetes (WHO, 1999) and, in their absence, categorisation is based on clinical presentation. For this reason some commentators subdivide Type 1 diabetes into two 'phenotypes': Type 1A which displays clear autoimmune involvement via the presence of antibodies; and Type 1B which displays idiopathic (spontaneous and unexplained) loss of β-cell function. However Lammi, Karvonen & Tuomilehto (2005, p.64) observe that:

> *"Whether these groups are really etiologically different can be debated, since the clinical presentation of both is similar and there may be genetic reasons for the lack of antibodies in some individuals or ethnic groups."*

In this study it is not possible to differentiate between the two phenotypes, therefore all analysis and reporting will be for Type 1 diabetes as a whole rather than subdivided, and Type 1 diabetes will generally be treated as an autoimmune phenomenon.

2.2.2 Gender and Type 1 diabetes

No pronounced differences in Type 1 diabetes incidences have been recorded by sex, although rates of illness tend to be slightly higher in males than females. The National Paediatric Diabetes Audit (a survey of childhood diabetes in England, Wales & Northern Ireland) reported that of their sample of 11,696 incident cases 52% were boys and 48% were girls (Diabetes UK, 2002).

2.2.3 Age and Type 1 diabetes

A major defining characteristic of Type 1 diabetes is that it is most often diagnosed in children and young adults. Indeed, half of people with Type 1 diabetes are diagnosed before 15 years of age and 90% have been diagnosed by the age of 30, with very few people diagnosed after 40 years old (Willliams & Pickup, 2004).

Figure 2.2 shows the age of the children sampled in the National Paediatric Audit at the time of their diagnosis (Diabetes UK, 2002). The number of children diagnosed was low in the first year of life, but then incidence increased rapidly, peaking between the ages of 2 and 4 years. There was a small decrease in incidence between the 5 and 6 years, which was followed by another peak between the ages of 7 and 10 years old. After the age of 10 years old, the number of incident cases dropped off markedly in the Audit data, which may reflect a genuine fall in incidence, but also may reflect that teenagers are less likely to be treated by paediatric services.

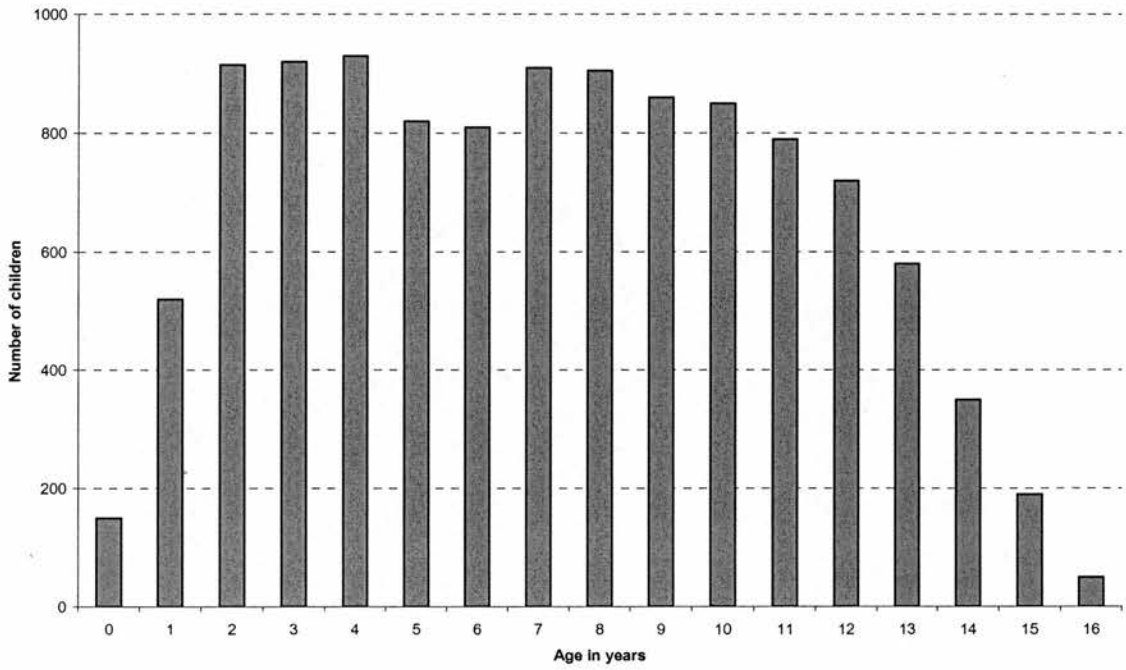


Figure 2.2 Age of diagnosis for children in the National Paediatric Diabetes Audit (taken from Diabetes UK, 2002, p.11)

A study by Staines, Bodansky, Lilley, Stephenson, McNally, & Cartwright (1993) also considered age of diagnosis in Yorkshire between 1978 and 1990 (Figure 2.3). Although the study is much older than the National Paediatric Audit in 2002, the authors standardised the data by reporting age-specific rates of incidence. Their data also suggested two peaks in incidence with the secondary peak being much higher than the first. The secondary peak also seems to have occurred slightly later for boys (13-17 years old) than for girls (9-13 years old).

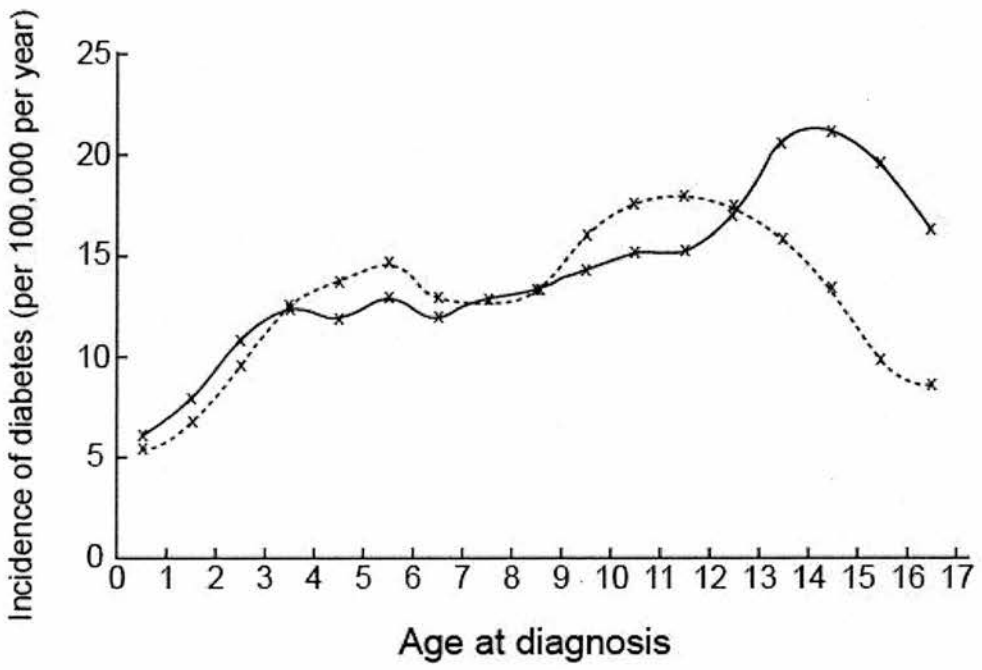


Figure 2.3 Type 1 diabetes incidence rate by age at diagnosis and sex. Solid line: male; dashed line: female. (Taken from Staines, Bodansky, Lilley et al., 1993).

Other published statistics that break Type 1 diabetes down by age are prevalence-based (which reflects the age at the time the data was collated) rather than incidence-based (which records age at the time of disease onset or diagnosis). Table 2.1 provides estimated numbers of people with Type 1 diabetes in the UK (in 2004) by age. The data show that the vast majority (71%) of the people with Type 1 diabetes were aged between 15 and 44 years old. However there was a sharp decline after the age of 44 which reflects the early mortality experienced by people with Type 1 diabetes, most of whom would have been diagnosed with diabetes over 30 years previously.

Age group	Diagnosed Type 1 diabetes	% of people with Type 1 diabetes in all age groups
0-14	14,000	5.9
15-44	170,000	71.6
45-64	49,000	20.6
65-74	4,000	1.7
75+	<500	<0.2
Total	237,500	100.0

Table 2.1 Estimated diagnosed Type 1 diabetes in the UK by age in 2004 (Diabetes UK, 2004).

2.2.4 Causes of Type 1 diabetes

Over the last three decades it has become increasingly clear that Type 1 diabetes is an autoimmune phenomenon, built upon underlying genetic susceptibility, and triggered by environmental factors. This section will review the evidence for this model of disease pathogenesis and the environmental factors that have been associated with Type 1 diabetes to date.

2.2.4.1 Genetic Susceptibility to Type 1 diabetes

It is generally accepted that Type 1 diabetes develops as a result of genetic susceptibilities combined with a variety of unknown environmental insults. The importance of genetic susceptibility is evident in the results of family and twin studies which have shown that people directly related to a person with Type 1 diabetes have a greater risk of developing the Type 1 form of diabetes themselves. In 1997, Lamb reported that the risk in the UK population of developing Type 1 diabetes was 0.2%, but for children of parents with Type 1 diabetes the risk was 4%, and for siblings of a person with Type 1 diabetes the risk was 8%. These findings are corroborated by other studies in the developed world which have found the risk for children of parents with Type 1 diabetes to be 4.8% (Tillil & Kobberling, 1987) and the risk for siblings to be between 4-8% (Gamble, 1980; Gottlieb, 1979; Tarn, Thomas, Dean, Ingram, Schwarz, Bottazzo et al., 1988; Tillil & Kobberling, 1987). Clearly, the increased familial risk suggests that inherited genetic susceptibilities are involved in the development of Type 1 diabetes.

However, evidence from studies of monozygotic (identical) twins suggests that a person's genetics are not the decisive factor in the development of Type 1 diabetes. If one of a pair of identical twins develops Type 1 diabetes, the chance of the other twin developing the condition has been shown in concordance studies to be around 33%, ranging between 23-53% depending on the study (Kaprio, Tuomilehto, Koskenvuo,

Romanov, Reunanen, Eriksson et al., 1992; Kumar, Gemayel, Deapen, Kapadia, Yamashita, Lee et al., 1993; Kyvik, Green, & Beck-Nielsen, 1995; Verge, Gianani, Yu, Pietropaolo, Smith, Jackson et al., 1995). This suggests that environmental factors must also be very important in the pathogenesis of the disease. Indeed, this level of concordance probably over-exaggerates the influence of genetics as twins are likely to share childhood environments and have similar environmental exposures.

Trying to determine the genetic component to Type 1 is a difficult process of deduction: the complex pattern of inheritance, the relatively high frequency of non-familial disease, and the increasingly rapid reduction of risk for first-, second- and third-degree relatives all suggest that multiple loci are involved.

To date the largest defined effect on susceptibility has been credited to the major histocompatibility complex (MHC), known as the human leukocyte antigen (HLA) system, which modulates the immune defence system of the body. The MHC is a collection of genes on a particular stretch of DNA on chromosome 6. The MHC genes encode secreted proteins with important immune properties and glycoproteins, which are expressed on the surface of cells and present antigens (any substance that elicits an immune response, usually harmful foreign bodies) to T lymphocytes (a type of white blood cell): this has a key role in immune responses. However, the MHC is highly polymorphic (genetically diverse) which presents significant difficulties in understanding the genetic inheritance of Type 1 diabetes, and even in individuals with similar genetic encodings of the MHC, the MHC will present and modulate immunity differently (Goldsby, Kindt, & Osborne, 1999).

Thus, the presence of certain MHC proteins conveys an increased risk of developing Type 1 diabetes (Bell & Hockaday, 1996). Despite the polymorphism, whole groups of MHC genes or 'haplotypes' tend to get passed down to progeny. Each person has two haplotypes: one from their father and one from their mother. It is now known that over 90% of Caucasian people with Type 1 diabetes carry the haplotypes DR3 and/or DR4 (Bell & Hockaday, 1996). The relative risk of carrying each haplotype can be calculated by comparing the frequency of the haplotype in a population of diabetes sufferers with the frequency in the general population. A relative risk of 1 would mean the haplotype is present in the same frequency in diabeties sufferers as in the wider population (Goldsby, Kindt, & Osborne, 1999). Haplotype DR3 confers a relative risk of about 7, and DR4 confers a risk of about 9. DR3/4 heterozygotes, who inherit a copy of both DR3 and DR4, have a relative risk of 14 showing the presence of the haplotypes have an additive effect (Bell & Hockaday, 1996). Conversely the presence of DR2 and some DQ haplotypes, which have a similar role to DR3 and DR4, have been observed as having a protective effect on the risk of developing Type 1 diabetes (Bell & Hockaday, 1996). However the link between these haplotypes and Type 1 diabetes is not thought to be as direct as inferred here, but rather the haplotypes are often transmitted to progeny along with other (unknown) genes that cause the disease. Thus around 50% of the Caucasian population carry either DR3 or DR4 haplotypes and the vast majority do not develop diabetes.

2.2.4.2 Immune mechanism in Type 1 diabetes

The body has two classes of immunity that protect the host against infection. Innate immune defence mechanisms protect the host against broad ranges of micro-organisms but not against specific organisms. The adaptive immune defence, however, tailors a specific response to individual pathogens. This immune response both combats the original infection, and provides long-lasting protection against re-infection by producing long-living 'memory' cells specific to the antigen. In autoimmune phenomena, adaptive immune defence mechanisms are thought to play a major role, falsely recognising certain host cells as foreign, attacking them and consequently destroying them. However, innate and adaptive immune responses are highly integrated and thus innate mechanisms are also likely to have some role in the onset of Type 1 diabetes.

In Type 1 diabetes there is evidence to suggest that there is a failure of immune self-tolerance towards the pancreatic β-cells by the T-lymphocyte (T) cells which form the mainstay of adaptive immunity. The pancreata of people with Type 1 diabetes who die close to the time of diagnosis have been observed to have lymphocytic infiltrate (Janeway, 1997). The lack of such infiltrate in diabetes sufferers following total β-cell destruction suggests that the immune response is driven by the recognition of β-cell autoantigens (Harrison, Colman, Dean, Baxter, & Martin, 1985). Furthermore, hemipancreatic grafts from an identical twin without Type 1 diabetes, into a sibling diagnosed with the disease many years before, is followed by the rapid loss of β-cell

function (Sibley, Sutherland, Goetz, & Michael, 1985). This rapid destructive process is β-cell specific, the other islet and pancreatic cells are unharmed, and accompanied by infiltrate which is dominated by effector T cells.

The way T cells work is to elicit a powerful response to the specific antigens they recognise. As with other lymphocytes, each has a unique set of receptor genes that are expressed as a unique cell-surface. This cell-surface functions as the antigen receptor, the form of the cell-surface determining which specific antigen the lymphocyte will recognise. Although each lymphocyte can only recognise one specific antigen, a huge repertoire of lymphocytes are developed with antigen receptors of near infinite diversity. In this way T cells and lymphocytes offer immunity against most antigens and can counter the rapid mutation of microorganisms. In particular, T cells can recognise when specific antigens are residing in the cytoplasmic compartment of other cells. The T cell's antigen receptors are sensitive to peptide fragments bound to the MHC molecules of other cells. The MHC molecules consist of three polypeptide chains: an α- and β-chain, and a third chain that incorporates an antigen peptide fragment. This third chain, when in place, provides a co-stimulatory signal for the T cell to recognise and bind to.

There are two types of T cells: T helper (T_H) lymphocyte cells and T cytotoxic (T_C) cells. When a T_H cells finds and binds to an antigen it mediates the immune response to the antigen. The bound T_H cell becomes an effector cell and responds in two ways: it proliferates more 'memory' T_H cells with the same antigenic specificity; and it secretes cytokines that activate the many and varied agents of both the innate (including

microphages, B-lymphocytes) and adaptive (T_C cells and other T_H cells) immune system which search, destroy, and remove all the instances of the antigen in the vicinity. The T_H cells are therefore considered to be very important for initiating and mediating many autoimmune phenomena, including Type 1 diabetes (Goldsby, Kindt, & Osborne, 1999).

The cytokines from the T_H cells also have a role in mediating B-lymphocytes (B) cells. B cells are also antigen specific, and will internalise its antigen. At this point a T_H cell will bind to it and secrete cytokines that induce the B cell to proliferate, creating new 'memory' B cells with its own antigenic specificity and antibody-secreting plasma cells. The antibodies from the plasma cell will then circulate, 'coating' antigens to stop them from binding to host cells and marking the antigen for destruction. However, autoreactive antibodies are also commonly produced as part of autoimmune phenomena. Antibodies directed against islets cells, insulin, and GAD are commonly found in people with Type 1 diabetes (WHO, 1999).

The T_C cells may also have a role in certain autoimmune processes. Once activated by cytokines from the T_H cells, they find the body's own cells which are infected or damaged (for example by a virus or a tumour). The T_C cells bind to the 'altered self-cells' and initiate lysis (cell destruction), whilst also proliferating more 'memory' T_C cells to guard against future re-infection (Goldsby, Kindt, & Osborne, 1999). Therefore if T cells falsely recognise β-cell autoantigens, the T_C cells may be employed in the direct destruction of the cells expressing the autoantigen.

To conclude, the exact immune mechanism for the development of Type 1 remains unknown and, indeed, the mechanism may be different depending on the triggering environmental factors. However both lymphocytic infiltrate and autoantibodies of the islet cells are found in people with Type 1 diabetes, suggesting a malfunction of T cell antigen recognition. In section 2.2.4.1 the observed relative risk is shown to increase for individuals who have certain haplotypes belonging to the DR region of the MHC genes, and the relative risk of developing Type 1 diabetes also increases (Bell & Hockaday, 1996). Although caution is necessary, this region of the MHC is generally responsible for encoding glycoproteins that are expressed onto specific cells of the host and which present antigen peptides to T cells. The T cell specific to a given antigen will only become active once it has been presented in this way by these MHC glycoproteins. Once T cells have been identified, antigens will continue to proliferate and mediate other immune responses until the antigen is no longer present (Yoon & Jun, 2000). Thus if MHC cells present a pancreatic β-cell autoantigen, and the T-cells accepts, this synergistic relationship between the MHC gene encoding and the host repertoire of T cells would plausibly result in diabetes.

Furthermore, the way the adaptive immune system responds to challenges is dynamic, and the repertoire of T cells in the host is influenced by previous exposures to antigens. Therefore, previous exposures to microbial infections will affect the autoimmune status of the individual making an autoimmune response either more or less likely. To this end, section 2.2.4.3a reviews the evidence concerning how viral infection may induce Type 1 diabetes, and section 2.2.4.4 (*Hygiene hypothesis*) considers the possibility that previous exposures to certain microbes have a protective effect against diabetes.

2.2.4.3 Environmental factors and the development of Type 1 diabetes

As discussed above (section 2.2.4.1), there is compelling evidence from familial and twin studies that environmental exposures play a significant role in the development of Type 1 diabetes. The environmental factors that initiate the autoimmune response in people with diabetes are still moot but there is a growing list of candidates considered here.

2.2.4.3a Viruses

The ability of microbial infections to elicit an adaptive immune response and therefore consequently modify future parameters of immunogenicity within the host, have meant that they have been considered good candidates for involvement in the aetiology of Type 1 diabetes for many years.

Viruses in particular have garnered much attention (Filippi & von Herrath, 2005; Hyöty & Taylor, 2002; Jun & Yoon, 2003; Yoon & Jun, 2000). The strongest evidence for viral involvement in the aetiology of Type 1 comes from animal studies carried out under laboratory conditions, where a number of viruses which result in the onset Type 1 diabetes have been identified (Lammi, Karvonen, & Tuomilehto, 2005). In humans, with the exception of congenital rubella (McEvoy, Cooper, Rubinstein, Fedun, & Ginsberg-Felner, 1986; Patterson, Chandra, & Jenson, 1981; Schopfer, Matter, Flueler,

& Werder, 1982), the results are not yet as clear. Despite the evidence in humans not being overwhelming, it is at least converging. Enteroviruses, which enter the host through the gastro-intestinal tract, are the subjects of the majority of studies and the Coxsackie virus has been considered a prime candidate in the development of diabetes for some time now (Frisk, Friman, Tuvemo, Fohlman, & Diderholm, 1992; Gamble, Taylor, & Cumming, 1973; Mertens, Gruneklee, & Eggers, 1983; Skarsvik, Puranen, Honkanen, Roivainen, Ilonen, Holmberg et al., 2006). However, there is also evidence that other enteroviruses, such as echovirus (Díaz-Horta, Bello, Cabrera-Rode, Suárez, Más, García et al., 2001; Frisk, Nilsson, Tuvemo, Friman, & Diderholm, 1992) and rotavirus (Honeyman, Coulson, Stone, Gellert, Goldwater, Steele et al., 2000) may also be able to elicit the onset of the condition. Other types of virus, such as Cytomegalovirus (CMV) (Pak, Eun, McArthur, & Yoon, 1988) and mumps virus (Helme, Otten, & Willems, 1980) have also been positively linked to the onset of Type 1 diabetes. Table 2.2 provides a comprehensive list of viruses that have been associated with Type 1 diabetes either in human or animal studies.

Table 2.2 Viruses associated with Type 1 diabetes in humans and animals after Hyöty & Taylor (2002, p. 1354) and Jun & Yoon (2003, pp. 9-10).

Virus	Host	Remarks
Coxsackie virus	Mice	Virus was passaged in murine beta cells before infection; cytolytic destruction of beta cells leading to IDDM.
	Nonhuman primates	Virus was passaged in monkey beta cells before infection; development of transient IDDM.
	Humans	Evidence of an association from epidemiological studies and anecdotal reports.
Echovirus	Humans	Evidence of an association from epidemiological studies.
Encephalomyo-carditis virus	Mice	Cytolytic destruction of beta cells leading to IDDM; macrophages paly a critical role in beta cell destruction in low dose infections.
Mengo virus	Mice	Cytolytic destruction of beta cells.
Retrovirus	Mice	Association of beta cells-specific expression of retroviral gene with the development of insulitis and IDDM in NOD mince.
	Humans	The evidence in humans is more controversial, but also thought to be associated with beta cell-specific expression of retroviral gene and development of human autoimmune IDDM.
Rubella Virus	Hamsters	Possible association with autoimmune IDDM.
	Humans	Follows intrauterine infection in offspring. Diabetes appears in 20% of cases after long time intervals. Islet cell antibodies induced. Vaccination has attenuated risk.

Mumps virus	Humans	Many early reports but role not confirmed. Possible induction of islet cells autoantibodies. Vaccination has attenuated risk.
Bovine viral diarrhoea-muscosal disease virus	Cattle	Suspected autoimmune response.
Reovirus	Mice	Possible association with autoimmunity and diabetes in mice.
Rotavirus	Humans	Reports of islet autoimmunity in children after rotavirus infection.
Kilham rat virus	Rats	No distinct infection of rat beta cells, but development of beta cell-specific autoimmunity leading to IDDM.
Cytomegalovirus	Humans	Association with autoimmune IDDM, but only thought to have a role in small number of cases.
Epstein-Barr virus	Humans	Associated with other autoimmune diseases, possible induction of autoimmune IDDM

One explanation of how viruses and other microbial infections may trigger autoimmunity is that some infection may result in direct cytolysis (cell destruction by breaking down its outer membrane) of infected cells with no involvement of the immune system. A number of viruses are able to infect the pancreatic β-cells and some, like encephalomyocarditis, have been observed to result in direct β-cell cytolysis in mice (Jun & Yoon, 2001). In humans, Coxsackie B virus strains have also been shown to directly infect β-cells and precipitate lysis (Roivainen, Rasilainen, Ylipaasto, Nissinen, Ustinov, Bouwens et al., 2000), although other observations of Coxsackie B4 virus have shown that tissue damage associated with such an infection can result in the release of islet autoantigens by the β-cell and consequently destruction by autoimmune response (Horwitz, Ilic, Fine, Rodriguez, & Sarvetnick, 2002).

An alternative hypothesis, known as 'molecular mimicry', reasons that if a person is exposed to viruses or bacteria which carry peptides very similar to the body's own, the consequent immune reaction may be cross-reactive for both the original antigen and any self-cells that express the similar autoantigen (Maclaren & Atkinsson, 1997). Coxsackie B4 virus carries a peptide sequence that is very similar to that found on a type of GAD (GAD65) found in the β-cell islets (Kaufman, Erlander, Clare-Salzler, Atkinson, Maclaren, & Tobin, 1992). However attempts to create cross-reactive T-cells to Coxsackie B4 and GAD *in vitro* have failed (Denman & Rager-Zisman, 2004), and molecular mimicry remains unproven.

Some pathogens have also been shown to have the ability to cause the expression of the co-stimulatory signals on tissue cells (which normally signals to T cells that an antigen is present), and the B7-1 co-stimulator has been shown to accelerate the rate of autoimmune disease in the pancreatic β-cells of non-obese diabetic (NOD) mice (Wong, Guerder, Visintin, Reich, Swenson, Flavell et al., 1995).

It has also been hypothesised that viral infections can damage the balance between two types of helper T cells. T_H cells differentiate into two types, T_H1 and T_H2 cells, with opposing cytokine profiles and effector functions (Mosmann, Cherwinski, Bond, Giedlin, & Coffman, 1986). The two cytokine profiles have very different effects on the type of immune stimulation they promote. For example, cytokines in the T_H1 response are thought to increase the killing efficacy of the macrophages and the proliferation of T_C cells, therefore an over abundance of T_H1 cells may favour the development of autoimmune disease. Conversely, T_H2 cells express a variety of cytokines, many stimulating the proliferation of B cells and increase antibody production, and which are thought to play an important role in the development of allergic diseases such as asthma and hay fever. The two profiles also have a cross-regulatory function, whereby the cytokines from T_H 1 will induce further T_H1 activity and oppress T_H2 activity, and vice versa (Azar, Tamim, Beyhum, Zouhair Habbal, & Almawi, 1999). This suggests that as external stimuli elicit an adaptive immune response, the T_H cells will differentiate into T_H1 and T_H2 according to the nature of the stimuli and the T_H1 and T_H2 cytokines already present. Thus the balance of the helper cells would seem to be able to change over time from one program to the other, ranging

from polarisation to either T_H1 and T_H2 with any number of intermediate positions (Kelso, 1995; McFarland, 1996).

.

According to this hypothesis, an imbalance towards T_H1 cells would increase the likelihood of Type 1 diabetes, and an imbalance towards T_H2 cells would protect against diabetes. However, it is becoming increasingly apparent that this understanding of the roles of T_H1 and T_H2 cells in the development of autoimmune disease is inadequate. The main supporting evidence for the hypothesis was provided by studies of non-obese diabetic (NOD) mice in which the direct cytotoxic effects and indirect mediation on β-cells destruction by cytokines were observed (Pennline, Roque-Gaffney, & Monahan, 1994; Rapoport, Jaramillo, Zipris, Lazarus, Serreze, Leiter et al., 1993). However, other studies have reached contrary conclusions (Anderson, Cornelius, Jarpe, Winter, & Peck, 1993; Lee, Wogensen, Shizuru, Oldstone, & Sarvetnick, 1994), suggesting that T_H2 cells may also play some role in the development of diabetes, rather than being merely 'protective' as first thought. Therefore, although it is clear that T_H1 and T_H2 have a role in the mediation of autoimmune disease, it is much more complex than was first supposed, as Azar, Tamim, Beyhum et al (1999, p. 308) conclude in their review:

> *"The previous assignment of a pathogenic role to T_H1 cells and a protective role to T_H2 cells and their respective cytokines in the pathogenesis and progression of IDDM was largely based on artificial conditions. This did not reflect the delicate balance and relative contribution of each T_H subset at distinct stages of the*

disease. Accordingly T_H1 cells are not the sole instigators of IDDM, and T_H2 cells are more harmful than previously believed."

This does not negate the fact that T_H1 and T_H2 profiles are involved in the pathogenesis of Type 1 diabetes. However the T_H1/T_H2 model as previously understood does not hold, and indeed, there is a lack of epidemiological evidence to support it (Dales, Chen, Lin, & Karsh, 2005; Olesen, Juul, Birkebaek, & Thestrup-Pedersen, 2001; Sheikh, Smeeth, & Hubbard, 2003).

2.2.4.3b Dietary factors

A number of dietary compounds have been implicated as aiding the development of Type 1 diabetes. Some food compounds, including wheat (Scott, Sarwar, & Cloutier, 1988), soy (Hoorfar, Scott, & Cloutier, 1991), cows' milk proteins (Elliott & Martin, 1984), and N-nitroso (compounds formed from nitrites found in meat products and the nitrates from vegetables; Helgason, Ewen, Ross, & Stowers, 1982), have been shown to increase the incidence of Type 1 diabetes in murine studies, most often using diabetes prone BB rats. Other compounds, such as coffee (Virtanen, Rasanen, Aro, Ylonen, Lounamaa, Akerblom et al., 1994), and again N-nitroso (Helgason & Jonasson, 1981) and cows' milk (Dahl-Jorgensen, Joner, & Hanssen, 1991; Fava, Leslie, & Pozzilli, 1994; Scott, 1990) have been implicated in epidemiological studies.

Of these compounds, N-nitroso and cows' milk protein are considered the most likely risk factors for Type 1 diabetes, because of the associations found in both animal and human studies (Åkerblom & Knip, 1998). N-nitroso compounds have been associated with the development of Type 1 diabetes in young rodents, and have also been linked by epidemiological studies to: the intake of smoked/cured mutton in Iceland (Helgason & Jonasson, 1981), food with high concentrations of nitrate and nitrite in Sweden (Dahlquist, Blom, Persson, Sandstrom, & Wall, 1990), and the high nitrate content of drinking water in Yorkshire (Parslow, McKinney, Law, Staines, Williams, & Bodansky, 1997).

The mechanisms linking cows' milk and feeding formulae based on cows' milk are as of yet poorly understood, and despite 20 years of study, there is still controversy regarding the legitimacy of the relationship (Åkerblom & Knip, 1998). However what is known is that, at least in the developed world, cows' milk contains the first foreign proteins that many infants ingest and therefore provide one of the first tests of the child's developing immunity. Indeed, there are plenty of suspect proteins in cows' milk that have been linked to Type 1 diabetes. Newly diagnosed people with Type 1 diabetes have been recorded as having enhanced innate and adaptive immune responses to bovine serum albumin (BSA) (Karjalainen, Martin, Knip, Ilonen, Robinson, Savilahti et al., 1992; Miyazaki, Cheung, Gaedigk, Hui, Van der Meulen, Rajotte et al., 1995). The homologous structural similarity between BSA and a type of islet cell antigen (ICA69) has been suggested as a possible explanation for the immune response. Similarly the beta casein protein in cows' milk also shows structural similarity to an eyelet cell protein called glucose transporter 2 (GLUT-2), although GLUT-2 is not

known as an autoantigen in Type 1 diabetes (Åkerblom, Vaarala, Hyoty, Ilonen, & Knip, 2002). Indeed, β-lactoglobulin (BLG) has also been found to induce an enhanced immune response in newly diagnosed patients with Type 1 diabetes (Savilahti, Ormala, Saukkonen, Sandini-Pohjavuori, Kantele, Arato et al., 1999; Vaarala, Klemetti, Savilahti, Reijonen, Ilonen, & Akerblom, 1996). The last suspect, bovine insulin, is also present in cows' milk and children who display β-cell autoimmunity tend to have a greater number of antibodies to bovine insulin than their controls (Vaarala, Knip, Paronen, Hamalainen, Muona, Vaatainen et al., 1999; for a review see Åkerblom, Vaarala, Hyoty et al., 2002)

It has also been observed that breastfeeding frequency and duration seem to have a protective effect against Type 1 diabetes. The first study, in Copenhagen (Denmark) found that mothers reported that children who developed Type 1 diabetes were breast fed for a shorter period of time than their healthy siblings (Borch-Johnsen, Joner, Mandrup-Poulsen, Christy, Zachau-Christiansen, Kastrup et al., 1984). These finding have now been confirmed by studies in many other countries (for a short review see Åkerblom & Knip, 1998). However what is not clear is whether breast feeding is indeed protective or whether early breast feeding cessation exposes the child to cows' milk based products.

2.2.4.4 Hygiene hypothesis

Although there is evidence linking certain microbial infections to the development of Type 1 diabetes (see section 2.2.4.3a *Viral Infections*) there is also mounting epidemiological evidence that infections in early childhood may be associated with a reduced risk of developing diabetes. Indeed, an infection (such as a virus) may induce, protect against or have no effect on the development of diabetes depending on the autoimmune status of the individual, determined by genes, age, and previous history of infection (Bach, 2005; Filippi & von Herrath, 2005). Building upon this understanding, the 'hygiene hypothesis' suggests that early life exposure to common infections may have profound effects on the development of the adaptive immune system, making a mal-response less likely. In this model, early exposure modifies the lymphocytic response to later immunological challenges (see section 2.2.4.2), and this adaptation decreases the likelihood of auto-antigen recognition. Therefore, children with reduced exposure to microbial antigens are expected to be more susceptible to developing Type 1 diabetes and children with increased exposure are less susceptible.

The hypothesis has been supported by animal studies of rats and mice where the incidence of Type 1 diabetes is higher among those reared in pathogen free environments (Leiter, Serreze, & Prochazka, 1990) and lower among those that have been exposed to viral or bacterial infection in early life (Schwimmbeck, Dyrberg, & Oldstone, 1988; Wilberz, Partke, Dagnaes-Hansen, & Herberg, 1991). Suggestively,

childhood infections have been shown to be associated with a reduced risk of Type 1 diabetes (Gibbon, Smith, Egger, Betts, & Phillips, 1997; Pundziute-Lycka, Urbonaite, & Dahlquist, 2000), and attendance at day-care has been observed to have a protective effect for young children (EURODIAB, 2000; McKinney, Okasha, Parslow, Law, Gurney, Williams et al., 2000).

In the UK, in the absence of reliable ecological data for infections (indeed, it is not known which infections should be considered were such data available), ecological studies have used measures of 'population mixing' as a proxy for infection: the dual premise being that interaction within a population creates greater potential for the circulation of infection and a turnover of new people within the population will bring new infections with them from their origins. To this end, epidemiological studies have considered population density, the presence of immigrants and the diversity of immigrant origins as indicative of population mixing. The general finding that Type 1 diabetes incidence is higher in rural areas with low population densities (Waugh, 1986), and less household overcrowding (Staines, Bodansky, McKinney, Alexander, McNally, Law et al., 1997) supports an assertion that closer living and interaction within a population may be protective against Type 1 diabetes. Furthermore, Parslow, McKinney, Law & Bodansky (2001) have also shown diabetes incidence to be lower in areas where child migrants arrive from a greater diversity of origins.

Finally, some authors (e.g. Strachan, 1989) have suggested that the development of T_H1/T_H2 cell profiles may provide the mechanism underpinning the hygiene hypothesis. However, this argument mainly occurs in literature regarding the

production of atopic diseases (e.g. hay fever, allergic asthma, eczema) rather than diabetes, and supposes that early exposure to infection results in maturation of the immune profile away from T_H2 to T_H1 cells. If one agrees with the summation that a T_H1 dominated profile is less likely to lead to atopy and more likely to lead to the development of autoimmune diseases (which as previously discussed is probably an oversimplification, see section 2.2.4.3a), then this would suggest that increased early exposure to infection would result in more diabetes, not less, which does not appear to fit the epidemiological evidence.

2.3 Type 2 diabetes mellitus

2.3.1 Introduction to Type 2 diabetes

In October 2004 Diabetes UK, estimated that there were 130,000 people in Scotland with Type 2 diabetes and 1.5 million people with Type 2 diabetes in the UK as a whole (2.6% of the UK population). Since then, the organisation has further increased their estimates for the total prevalence of diabetes (Type 1 and 2) in the UK to around 2 million people (Diabetes UK, 2005b), following the publication of the PBS Diabetes Population Prevalence Model for England (Yorkshire & Humber Public Health Laboratory, 2005). They are yet to publish a breakdown of this total estimate by diabetes Type, but given that 87.5% of people with diabetes in the UK have Type 2 diabetes (Diabetes UK, 2004) this would mean that some 1.75 million people in the UK have Type 2 diabetes which would equate to around 3.0% of the UK population.

Type 2 diabetes can result either from a loss of ability to produce insulin or as a consequence of insulin resistance, but both are usually present when the condition becomes clinically manifest (WHO, 1999). Typically, Type 2 diabetes is preceded by insulin resistance and impaired glucose tolerance (IGT). Once insulin resistance is pronounced, the development of diabetes will depend on the person's ability to secrete enough insulin to compensate for the decreased efficacy (Dabelea & Hamman, 2004). Therefore any accompanying loss of insulin production will result in increased blood

glucose levels. This chronic hyperglycaemia is thought to induce beta-cell apopotis (programmed cell death), irreversible insulin deficiency, and permanent diabetes (Silink, Kida, & Rosenbloom, 2003, p.3).

Type 2 diabetes is normally differentiated from Type 1 diabetes by a combination of clinical presentation and the absence of the autoantibodies that presage the latter. Type 2 diabetes normally affects people later in life – characteristically after the age of 40 (Diabetes UK, 2004) – and has formerly been known as 'late onset diabetes'. Disease progression of Type 2 is slower than for Type 1 diabetes, typically resulting in a less dramatic effect on blood glucose levels, which normally does not require injections of insulin. Therefore, Type 2 diabetes has also previously been known as 'non-insulin dependent diabetes' (NIDDM). However, both the terms of 'late onset diabetes' and 'non-insulin dependent diabetes' are misnomers when applied to Type 2 diabetes: although Type 2 diabetes is far more common in older people, the disease is found in small numbers in younger age groups, including children and teenagers (Diabetes UK, 2002; Ehtisham, Barrett, & Shaw, 2000; Fagot-Campagna, Narayan, & Imperatore, 2001). One study estimated that there are approximately 1,400 children with Type 2 diabetes in the UK (Lobstein & Leach, 2004). Similarly, some 13.6% of people with Type 2 diabetes have the severity of condition to require insulin therapy (McAlpine & Cunningham, 2004), and so can not be described as having NIDDM.

The severity of the hyperglycaemia experienced by people with Type 2 diabetes covers a very wide range with an accompanying range of treatments. As already intimated, for some people with Type 2 diabetes, the level of glycaemic dysfunction means they

require injections of exogenous insulin to survive. However most diagnosed people with Type 2 diabetes occupy a middle ground where their condition requires prescribed oral tablets to help control their blood glucose levels. People in the early stages of Type 2 diabetes do not require medication and can control the disease with dietary interventions and increased physical exercise. For many more people the onset and progression of the disease is slow and normal symptoms of hyperglycaemia are absent or so mild, they do not realise that they have the condition. Some of these people may be identified as having diabetes due to suspicions aroused based on familial risk or blood tests for other purposes (ABPI, 2005). Diagnosing diabetes for individuals with suspected Type 2 diabetes is carried out in the same manner as for Type 1 diabetes (see section 2.2.1) with a blood sample taken and tested for raised blood glucose level. However, if the individual is asymptomatic (often the case in Type 2 diabetes) a diagnosis should not be made on the basis of a single positive test and a second complimentary test is needed for confirmation: such as an overnight fasting blood sample or an OGTT (see page 11).

Due to the difficulties in identifying people with asymptomatic or very mild Type 2 diabetes, Diabetes UK (2004) have estimated that up to one million people in the UK may have undiagnosed Type 2 diabetes. Working from Diabetes UK's (2004) estimated population prevalence of Type 2 diabetes of 1.5 million, this suggests that for every three people diagnosed with Type 2 diabetes in the UK there are two people with undiagnosed Type 2 diabetes. Other sources in the UK and US suggest that the ratio of people with diagnosed diabetes to undiagnosed diabetes may actually be as high as 1:1 (Harris, 1989; Williams, Wareham, Brown, Byrne, Clark, Cox et al., 1995).

Furthermore, the determination of diagnosed Type 2 diabetes in a population is problematic, as the cases identified will depend on the dataset employed and the definition of Type 2 diabetes (Morris, Boyle, MacAlpine, Emslie-Smith, Jung, Newton et al., 1997).

2.3.2 Causes of Type 2 diabetes

The specific causes and pathogenic mechanisms of Type 2 diabetes are poorly understood and so the disease has come to be defined by an absence of autoimmune involvement and via its association with a number of observed risk factors. Type 2 diabetes results from the interaction of genetic, environmental and behavioural risk factors which, in recent times, have increasingly been conceptualised within a life course approach (Ben-Shlomo & Kuh, 2002). In this approach, the risk presented by these factors is specific to certain sensitive periods of a person's life. The risk of developing diabetes accumulates throughout life to a greater or lesser extent depending on the person's genetic susceptibility, environment and behaviour at certain times of their life (see Figure 2.4). Therefore Type 2 diabetes must be viewed as multi-factorial rather than as a heterogeneous condition and any number of separate disease processes, acting at various stages of life, may be involved in the pathogenesis of diabetes by the time it becomes clinically manifest (Müller-Wieland, Kotzka, & Goldstein, 2003).

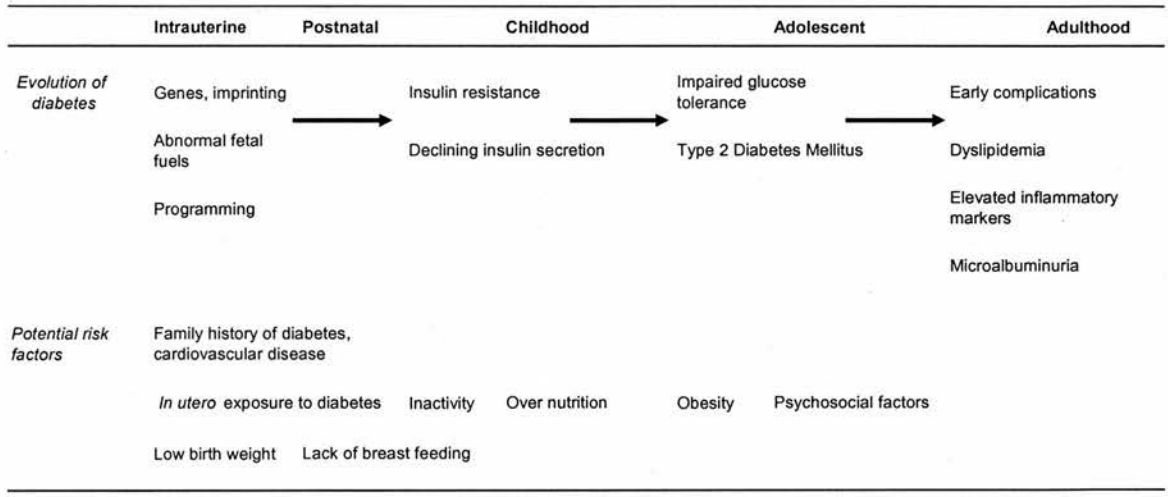


Figure 2.4 Risk factors for Type 2 diabetes mellitus from a life course prospective (taken from Dabelea & Hamman, 2004, p.790).

Figure 2.4 recognises a number of risk factors that operate within the foetal environment and early life, such as abnormal foetal fuels and *in utero* exposure to diabetes, which will be described in greater detail in the subsequent sections. Dabelea & Hamman (2004, p.790) note:

> *"Although the amount of diabetes in adulthood that can be attributed to such exposures is small, given that they are relatively infrequent, they all appear to act through increasing the risk for obesity at early ages. There is conclusive evidence that the persistence of adolescent obesity into adulthood increases with the earlier onset of obesity."*

There are many risk factors for Type 2 diabetes that operate in adulthood (a summary is included in Table 2.3), the most established of which will also be detailed in the following sections. However it is interesting to note the influence of both modifiable behavioural and cultural factors such as diet, obesity, physical exercise, smoking and psychosocial factors, as well as non-modifiable risk factors such as age, gender, ethnic group and family history.

Table 2.3 Risk factors associated with Type 2 diabetes. Variables shown in italics are not firmly established (after Dabelea & Hamman, 2004, p. 792)

Summary of Type 2 Diabetes Mellitus Risk Factors

Demographic variables
- Older age
- Male gender
- Ethnic group
- Family history of diabetes

Physiologic variables
- High glucose level (fasting & post challenge)
- Low insulin secretion
- Insulin resistance syndrome
- Hypertension
- *Low magnesium level*
- *Low chromium level*
- *High plasma non-esterified fatty acids*
- *Low sex hormone binding globulin*

Low physical activity

Cigarette smoking

Social status & *psychosocial* variables
- Social Deprivation
- Low social status
- Income inequality
- *Depression*

Obesity-related results
- High total adiposity
- Central fat distribution
- Higher intra-abdominal fat
- Longer duration of obesity
- Weight gain

Dietary variables
- High calorific intake
- Very low and *high* alcohol intake
- *High total and saturated fat intake*
- *Low fibre intake*
- *High glycaemic index foods*
- *Low vitamin D intake*
- *Low magnesim intake*
- *Low potassium intake*
- *Low polyunsaturated fat intake*
- *Low vegetable fat intake*
- *Low whole grain intake*

2.3.2.1 Gender, age, ethnicity and Type 2 diabetes

Age is thought to be a strong component of diabetes risk for two reasons. Firstly, older people have had more exposures to risk factors which cumulatively cause the physiological damage which leads to diabetes. Secondly, old age *per se* is likely to lead to a decline in ß-cell function and compound pre-existing insulin deficiency. One of the most comprehensive sources of clinical and epidemiological data regarding Type 2 diabetes in the UK is from the UK Prospective Diabetes Study (1988). The study identified 1857 newly presenting diabetes cases in 15 centres in the UK. In this sample there was a clear male preponderance with 54% more males than females being diagnosed with diabetes, despite the average age of onset being similar in men (51.4 yrs ± 8.6) and women (52.8 yrs ± 8.1).

However since the 1988 UK Prospective Diabetes Study, the average age of diagnosis is likely to have increased as the population has aged. Indeed, in a study conducted in Poole, (UK) between 1996 and 1998, the average age of diagnosis was 64.3 years old, with the male average being approximately a year and a half younger (62.9 years) than the overall average and the female average being approximately year and a half older (65.9 years) (Gatling, Guzder, Turnbull, Budd, & Mullee, Gatling, Guzder, Turnbull, Budd, & Mullee, 2001).

Figure 2.5 shows the increasing incidence of Type 2 diabetes with age in Poole, peaking for both males and females over the age of 60. The preponderance towards men, although less pronounced than suggested by the UK Prospective Diabetes Study (1988), is still clearly noticeable particularly between the ages of 50 and 80 years old.

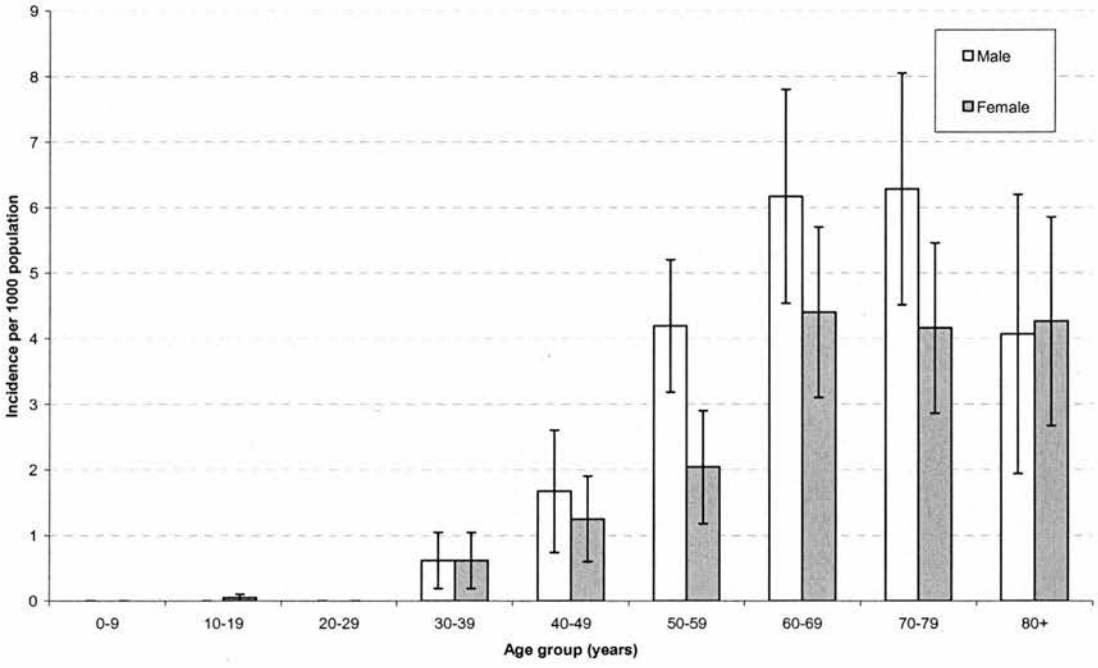


Figure 2.5 Annual age-specific incidence rates of newly diagnosed Type 2 diabetes by sex in Poole 1996-8 (taken from Gatling, Guzder, Turnbull et al., 2001, p.110).

In the Poole study a solitary (19 year old) female was diagnosed with Type 2 diabetes under the age of 30. Although there has been a reported increase in the number of young people developing Type 2 diabetes (Diabetes UK, 2002; Ehtisham, Barrett, & Shaw, 2000; Fagot-Campagna, Narayan, & Imperatore, 2001) this number is still

thought to be relatively small: one estimate suggested up to around 1,400 children in the UK (Lobstein & Leach, 2004). Given the lower awareness of Type 2 diabetes in young people at the time of the Poole study, it is possible that some diabetes in the younger age groups remained undiagnosed or mis-diagnosed as Type 1 diabetes.

It has been known for some time that the prevalence of diabetes is much higher in minority ethnic groups resident in the UK (Mather & Keen, 1985; Simmons, Williams, & Powell, 1991). At present, diabetes prevalence figures by ethnic group are not available for Scotland; during the latest national survey only 37% of known cases had their ethnicity recorded (Scottish Diabetes Survey Monitoring Group, 2004). However standardised percentage prevalence is available for England and is shown in Figure 2.6 by ethnic group. When compared to the general population, the figure clearly illustrates the three-fold higher prevalence of diabetes experienced by the black Caribbean and Indian populations, and the five-fold higher prevalence experienced by the Pakistani and Bangladeshi populations. In addition, the clinical onset of diabetes also occurs up to 10 years earlier in South Asians (Nicholl, Levy, Mohan, Rao, & Mather, 1986).

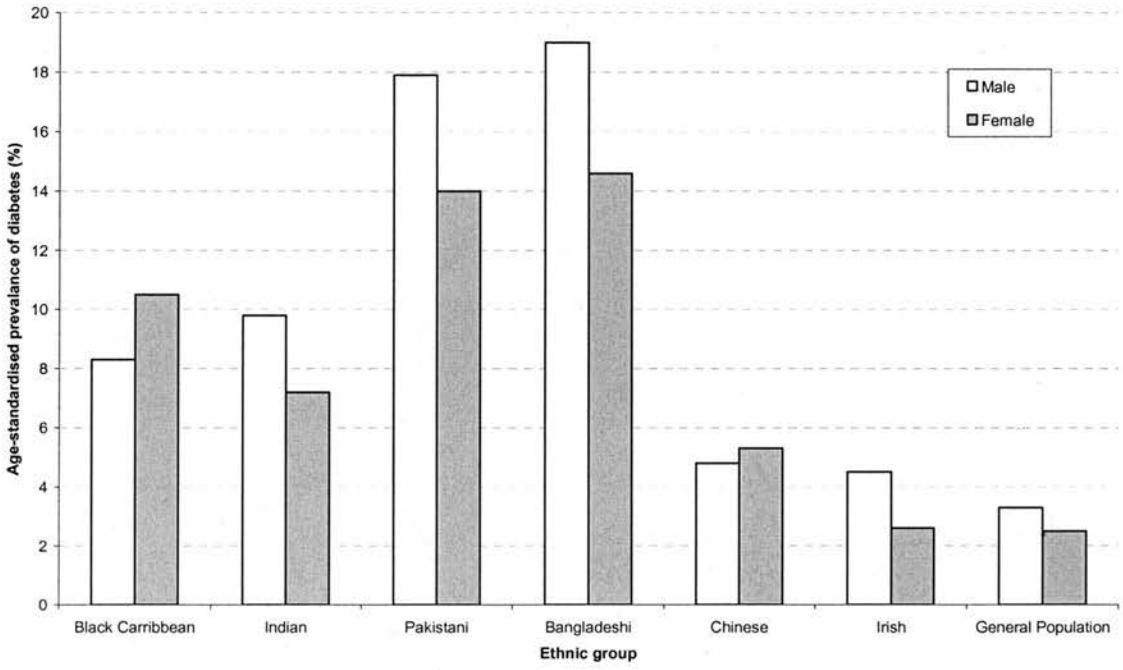


Figure 2.6 Prevalence of diagnosed diabetes by ethnic group in England, 1999 (source Joint Health Surveys Unit, 2001).

2.3.2.2 Genetic susceptibility to Type 2 diabetes

The variability of genetic susceptibility to Type 2 diabetes at the population level is supported by the different prevalence of the disease by ethnic group, as exemplified in section 2.3.2.1. At the individual level, the best evidence for a genetic link with diabetes comes from twin and familial studies. The concordance of Type 2 diabetes in monozygotic (identical) twins is thought to be around 40-50%, and 37% for dizygotic (non-identical) twins (Kaprio, Tuomilehto, Koskenvuo et al., 1992; Poulsen, Kyvik,

Vaag, & Beck-Nielsen, 1999), although concordance may be higher with lifelong follow-up (Medici, Hawa, Ianari, Pyke, & Leslie, 1999). A sibling of a parent with Type 2 diabetes has a 15% risk of developing the condition (Diabetes UK, 2004), and around 40% of newly diagnosed people with diabetes in the UK report having a close relative with the condition (UK Prospective Diabetes Study Group, 1988).

Despite the clear evidence of inherited genetic susceptibility, the search for specific genes associated with Type 2 diabetes has been inconclusive. The heterogeneous nature of the disease suggests a similar heterogeneity of associated genetic causes. This conclusion seems to be borne out by the results of genetic studies on various populations, each of which indicate candidate genes on different chromosomes: Mexican Americans (chromosomes 2 and 10); Swedish-speaking peoples in Botnia, Finland (chromosome 12); Pima Indians of Arizona, US (chromosome 11); and families of Northern European decent in Utah, US (Chromosome 1) (respectively Duggirala, Blangero, Almasy, Dyer, Williams, Leach et al., 1999; Elbein, Hoffman, Teng, Leppert, & Hasstedt, 1999; respectively Hanis, Boerwinkle, Chakraborty, Ellsworth, Concannon, Stirling et al., 1996; Hanson, Ehm, Pettitt, Prochazka, Thompson, Timberlake et al., 1998; Mahtani, Widen, Lehto, Thomas, McCarthy, Brayer et al., 1996).

In 1962 (republished 1999), Neel hypothesised that increased prevalence of diabetes in western and 'westernising' societies was associated to a 'thrifty genotype'. According to this argument, some people retain an ancestral genetic make-up suited to Paleolithic environmental conditions and are predisposed to low metabolic rates, sodium

conservation, and rapid mobilisation of insulin when carbohydrates are available (Sharma, 1998). People with this thrifty genotype will be more susceptible to developing obesity, hypertension and Type 2 diabetes. Other individuals who have more recent mutations to the relevant genes will have lost this thriftiness and will therefore be less susceptible to Type 2 diabetes. However, at present the 'thrifty gene' has not been identified and the hypothesis remains unproven (Dabelea & Hamman, 2004).

Genetic susceptibility interacts with environmental factors to cause impairment of glycaemic control which may eventually result in the development of Type 2 diabetes. Evidence for the important role of environmental factors comes from migrant studies, which have shown that migrants from countries with low prevalence of Type 2 diabetes experience increased risk of developing the condition once they have moved to countries with a higher prevalence. A classic example is provided by Hara, Egusa, Yamakido, & Kawate (1994) who observed that Japanese migrants living in Hawaii and Los Angeles have a three-fold increase in prevalence when compared to natives of Japan. Some non-migrant populations which have experienced rapid cultural change also experience rapid increases in the prevalence of Type 2 diabetes, often in the space of a few generations. The prevalence of diabetes in the Pima Indians of Arizona rose 40% between 1967 and 1977 (Bennett, Knowler, & Rushforth, 1979), a rise which can only be due to environmental factors.

.

2.3.2.3 Birth weight and Type 2 diabetes

A number of studies have shown a relationship between birth weight and the development of glucose intolerance and Type 2 diabetes (Hales, Barker, Clark, Cox, Fall, Osmond et al., 1991; Phipps, Barker, Hales, Fall, Osmond, & Clark, 1993; Valdez, Athens, Thompson, Bradshaw, & Stern, 1994). The central premise is that low birth weight reflects poor foetal nutrition *in utero.* Poor foetal nutrition is a function of maternal body size, uterine perfusion, placental function and foetal metabolism (Harding, 2001). As well as slowing foetal growth, nutritional deprivation *in utero* may also affect biological programming and foetal pancreatic development leading to increased risk of developing diabetes (Hales, 1992). In addition, the 'catch-up' growth that often follows low birth weight may also be related to an increased risk of diabetes The 'catch-up' hypothesis notes the relationship between low birth weight and adult obesity and, in particular, the increased risk of diabetes associated with people born of low weight who become overweight in childhood and early adulthood (Dabelea & Hamman, 2004).

An alternative hypothesis, which is thought to explain a small number of cases, suggests genetic susceptibilities relating to insulin resistance also predispose a child to low birth weight. It is this predisposition to insulin resistance, rather than the low birth weight *per se*, which may then progress to Type 2 diabetes. For example, a glucokinase gene mutation is thought to be responsible for a specific subtype of Type 2

diabetes known as maturity-onset diabetes of the young (MODY): persons with MODY are usually born a half a kilogram lighter than their unaffected siblings (Hattersley, Beards, Ballantyne, Appleton, Harvey, & Ellard, 1998).

The relationship of low birth weight and Type 2 diabetes highlights the importance of early life experiences in the future development of diabetes. In further support of this point, breast feeding has also been shown to be preventative both against obesity and Type 2 diabetes and the move from breast feeding to bottle feeding in the UK may play a small part in the increasing prevalence of the disease (Kramer, Barr, Leduc, Boisjoly, & Pless, 1985; Pettitt, Forman, Hanson, Knowler, & Bennett, 1997; von Kries, Koletzko, Sauerwald, von Mutius, Barnert, Grunert et al., 1999).

2.3.2.4 Diet, obesity, physical activity and Type 2 diabetes

Great emphasis has been placed on the role of western lifestyles in the development of diabetes as prevalence has increased worldwide. People in the post-industrial world have, on average, increased their calorific intake, are more prone to sedentarism, and are therefore more likely to be obese as a result. As such lifestyles proliferate, genetically susceptible people will find glucose homeostasis more difficult, and as a consequence develop Type 2 diabetes. As developing countries become more affluent and adopt more 'western' lifestyles, the prevalence of diabetes is expected to rise markedly (Wild, Roglic, Green et al., 2004).

The relationship between lifestyle risk factors and Type 2 diabetes is illustrated in Figure 2.7. Intake of excess food, particularly food of high calorific value, in combination with a lack of physical activity, leads to obesity. Obesity is pivotal to the development of insulin resistance, which results in raised blood glucose levels (Long, O'Brien, MacDonald, Leggett-Frazier, Swanson, Pories et al., 1994; Swinburn, Nyomba, Saad, Zurlo, Raz, Knowler et al., 1991). At this point, more insulin will need to be secreted to adjust for the lowered effectiveness of the insulin. If sufficient insulin cannot be manufactured in order to offset the efficacy of the hormone, chronic hyperglycaemia will result. Increased blood glucose can then directly damage β-cells and other sensitive cells (such as the retina of the eye, the kidneys or nerves) and eventually lead to their destruction (ABPI, 2005). Oxidative stress, has also been posited as a possible pathogenic mechanism to link insulin resistance, diabetes and cardiovascular disease. In this model the hyperglycaemia that results from insulin resistance is associated with an increase of deleterious free radicals and reactive oxygen species that damage β-cells and the vascular system (Ceriello & Motz, 2004).

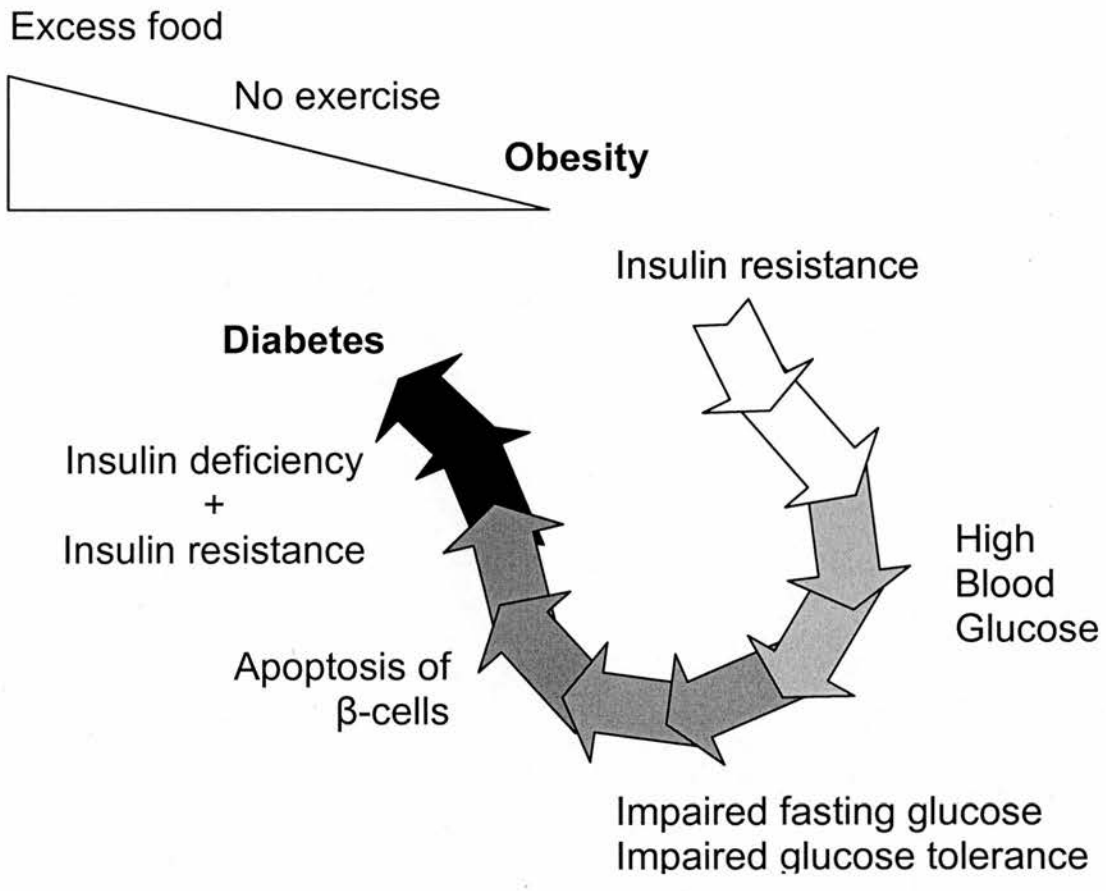


Figure 2.7 The effects of excess calories and a sedentary lifestyle in leading to the development of obesity, insulin resistance, impaired glucose homeostasis and, Type 2 diabetes (Silink, Kida, & Rosenbloom, 2003 p.3).

The relationship between Type 2 diabetes prevalence and being overweight has been confirmed in many countries (West & Kalbfleisch, 1971). Being overweight or obese are typically measured using the body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in metres. The

link between BMI and Type 2 diabetes is evident in the 2003 Scottish Diabetes Survey (Scottish Diabetes Survey Monitoring Group, 2004), where of the diabetes sufferers recorded, 80.2% had BMI scores classified as overweight (35.8%), obese (37.5%) or morbidly obese (6.9%). Where an individual stores fat is also an important independent risk factor of Type 2 diabetes: people prone to intra-abdominal fat deposition ('apple-shaped') are particularly at risk of developing diabetes (Carey, Walters, Colditz, Solomon, Willett, Rosner et al., 1997; Haffner, Stern, Mitchell, Hazuda, & Patterson, 1990; Ohlson, Larsson, Svardsudd, Welin, Eriksson, Wilhelmsen et al., 1985). It is now well established that obesity and insulin resistance result in a destructive cycle that leads progressively to increasing insulin deficiency and diabetes.

Dietary quality has also been shown to be associated with Type 2 diabetes. The consumption of saturated fat is particularly problematic and has been shown to induce insulin resistance and dyslipidemia (disordered lipid levels in the blood) in rats (Hunnicutt, Hardy, Williford, & McDonald, 1994). In Australia, a group of Aboriginals with Type 2 diabetes were taken to the outback where they hunted for their food, with the meat mainly coming from kangaroos (the meat is only 10% fat in the wild) and fish (Beck-Nielsen & Hother-Nielsen, 2004). Although there was very little weight loss in the group, their diabetes had almost disappeared. There is less evidence of other food compounds being associated with Type 2 diabetes, but candidates include: high-glycaemic index foods (Salmeron, Hu, Manson, Stampfer, Colditz, Rimm et al., 2001); refined grains (Liu, Manson, Stampfer, Hu, Giovannucci, Colditz et al., 2000) and magnesium, calcium and potassium (Colditz, Manson, Stampfer, Rosner, Willett, & Speizer, 1992). However, whole grains have been suggested as being inversely

related to both cardio-vascular disease and Type 2 diabetes (Liu, Manson, Stampfer et al., 2000).

Physical inactivity is not simply related to diabetes through reduced calorie expenditure. In the Nurse's Health Study in the US (Manson, Rimm, Stampfer, Colditz, Willett, Krolewski et al., 1991), weekly physical activity was shown to be protective against diabetes independent of obesity, and reduced the risk of developing diabetes by 20% compared to less active individuals. Modest increases in physical activity have also been shown to act against the development of diabetes even if the exercise is less than vigorous – i.e. walking (Helmrich, Ragland, Leung, & Paffenbarger, 1991; Hu, Sigal, Rich-Edwards, Colditz, Solomon, Willett et al., 1999).

2.3.2.5 Socio-economic status, area context, and psychosocial factors in the development of Type 2 diabetes

The socio-economic context within which people live their life has been linked to increased prevalence of many chronic diseases including Type 2 diabetes. In the UK and elsewhere, Type 2 diabetes has repeatedly been linked to the socio-economic status of either the individual or the area in which they live (Bhopal, Hayes, White, Unwin, Harland, Ayis et al., 2002; Connolly, Unwin, Sherriff, Bilous, & Kelly, 2000; Evans, Newton, Ruta, MacDonald, & Morris, 2000; Marmot, Smith, Stansfeld, Patel, North, Head et al., 1991; Meadows, 1995; Tang, Chen, & Krewski, 2003; Whitford, Griffin, & Prevost, 2003). Prevalence data for non-insulin treated Type 2 diabetes in England and

Wales are presented in Figure 2.8. The figure clearly displays a gradient with increasing deprivation quintile and the prevalence of Type 2 diabetes was 40% higher in the most deprived quintile than in the least deprived. Preponderance towards men is also evident: the prevalence being on average 30% higher for men that women, suggesting that men living in the most deprived areas are most at risk of developing Type 2 diabetes. At present there are no studies of the relationship between deprivation and Type 2 diabetes incidence, as incidence data is rarely collected in the UK.

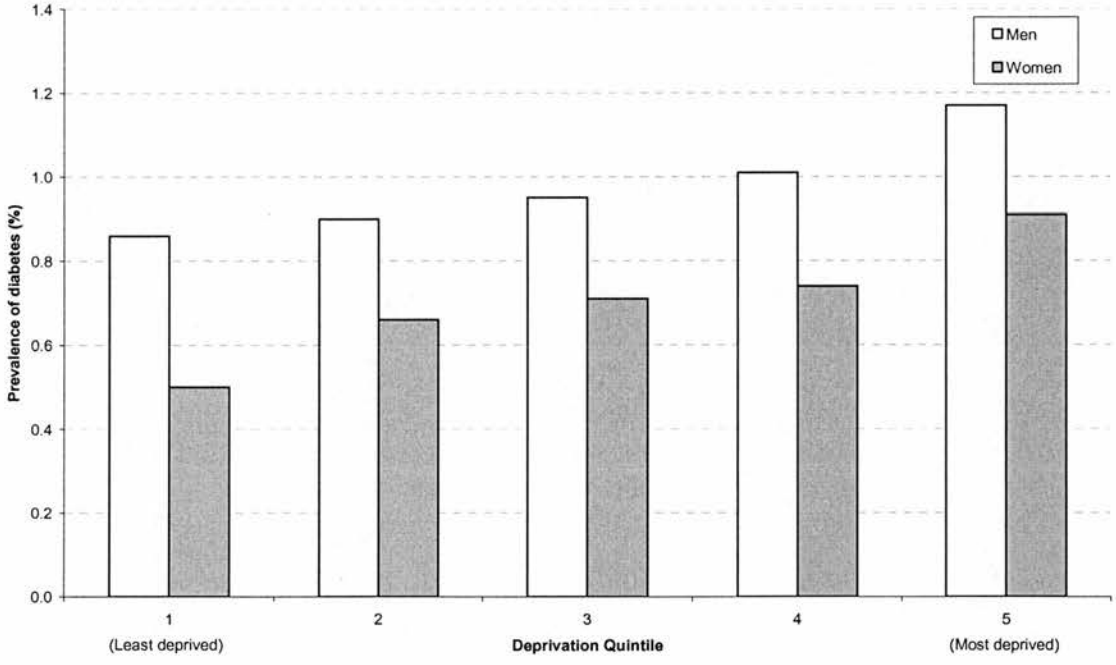


Figure 2.8 Prevalence of non-insulin treated Type 2 diabetes by deprivation category, 1994-98, England & Wales (source Office for National Statistics, 2000).

The reason for the relationship between socio-economic status and Type 2 diabetes prevalence is thought to be a relatively complex series of interactions between the individual and their environment. Over time, people are differentially exposed to both diabetogenic factors and protective factors depending on their socio-economic status, which affects their likelihood of developing diabetes. For example, in early life, low birth weight increases the likelihood of developing diabetes in later life (as discussed in section 2.3.2.3) and is known to be related to social class (Joffe, 1989). Later, in childhood and adulthood, diabetogenic behavioural factors such as increased food intake, poor diet (see section 2.3.2.4), and smoking are also more prevalent in people of lower socio-economic status (Billson, Pryer, & Nichols, 1999; Leather, 1996; Sargeant, Khaw, Bingham, Day, Luben, Oakes et al., 2001; Will, Galuska, Ford, Mokdad, & Calle, 2001). Meanwhile protective activities such as participation in sport are also less common in deprived areas (Macintyre & Ellaway, 1998).

Beyond the individual, the characteristics of where one lives may also affect the risk of developing diabetes. Local area context has a significant impact on health via a complex interplay of social, cultural and physical interactions which take place within and between local areas (Gatrell, Berridge, Bennett, Bostock, Thomas, Popay et al., 2004). For instance, although a person chooses what they may want to eat, this choice is affected by what food products are available to them in the area, the cost of these products, and by the prevailing food culture of the local area as well as wider societal norms. It has repeatedly been shown that deprived areas have less availability of affordable nutritious food: indeed the difficulty afforded to finding cheap non-processed food and has led to some British inner city areas being described as 'food

deserts' (Cummins & Macintyre, 2002; Lang & Caraher, 1998). Recent evidence suggests that the popular theory of deprived areas having more fast food outlets is actually false (Macintyre, McKay, Cummins, & Burns, 2005), although it is also clear that people who live in more deprived areas are more likely to eat food that is high in saturated fat, salt and sugar (Billson, Pryer, & Nichols, 1999). Similarly, unattractive and unsafe playgrounds and parks, high area crime rates, and high level of teenage antisocial behaviour are also likely to be at least partly responsible for the lower levels of participation in leisure activities and sport as observed in deprived areas of Glasgow (Ellaway & Macintyre, 2003; Macintyre & Ellaway, 1998).

From these examples, we can see that the increased risk of diabetes in people of low socio-economic status are not only the product of the individual lifestyle choices, but are also the product of the structural context of the area within which the choices are made. Building on the increased understanding of the role of context, some authors have taken matters further and studied 'socio-spatial' context, demonstrating that where one lives in relation to others also has an effect on health. Boyle, Gatrell, & Duke-Williams (1999; 2004) found relationships between deprivation variability and both standardised morbidity ratios and the reporting of limiting long-term illness in census wards in England and Wales, suggesting that people in wards with heterogenous levels of deprivation are more likely to experience ill health. As yet there have been no studies that investigate the effect of socio-spatial context of where one lives on the development of diabetes.

2.4 Treating, monitoring and the complications of diabetes mellitus

When treating both Types of diabetes, the main aim is to control and normalise blood glucose levels and blood pressure in order to negate the symptoms of hyperglycaemia and to avoid the long term complication of hyperglycaemia and hypertension (see Table 2.4 for common complications of diabetes). Ideally, blood glucose levels should be in the range of 4.0 - 7.0 mmol L^{-1} before meals, <10.0 mmol L^{-1} after meals, and around 8.0 mmol L^{-1} before bed (European Diabetes Policy Group, 1999a) and blood pressure should be <150/85 Hg (UK Prospective Diabetes Study Group, 1998c, , 1998d). The person's blood pressure should be monitored at each consultation and anti-hypertensive drugs are prescribed if blood pressure becomes raised. To maintain control of blood glucose, people with Type 1 diabetes inject with short-lived insulin before meals, to meet the carbohydrate challenge they are often presented with, and with long-lived insulin to increase background levels of insulin to maintain normal glucose levels in between meals and overnight (ABPI, 2005). With Type 2 diabetes, control of blood glucose is maintained via diet changes, oral tablets or injections of insulin. The exact treatment used will depend on the severity of the condition. Diets with more complex carbohydrates, and which are low in glucose, saturated fat and salt, are recommended for all patients with diabetes (including Type 1), as are physical exercise and weight loss, as they help control blood glucose levels.

Table 2.4 Common complications of diabetes mellitus (source Lundstrom, Mordes, & Rossini, 1998)

Complication	Organ	Description
Retinopathy	Eyes	Diabetic Retinopathy is a deterioration of the small blood vessels that nourish the retina. Although diabetic retinopathy is a serious cause of blindness, only a small percentage of persons with diabetic retinopathy lose their sight.
Nephropathy	Kidney	Diabetic nephropathy is a complication of long-term diabetes that results in damage to the bundles of capillaries that form the kidneys' filtering system. Diabetic nephropathy develops in stages over many years. Kidney filtering becomes less efficient, and certain proteins leak out. Protein in the urine may be the first sign of nephropathy. Other signs include high blood pressure, weight gain from fluid retention, fatigue, and just feeling ill. Kidney function tests help determine the degree of kidney damage. Treatments for kidney failure include haemodialysis (done at the hospital 3 times a week), peritoneal dialysis (done 3 to 4 times a day at home), and kidney transplants.
Neuropathy	Nerves	Nearly 70% of persons with diabetes experience some degree of nerve damage or neuropathy. Neuropathy occurs when constantly high blood sugar destroys both nerve fibre (axon) and the fatty insulation that surrounds it (myelin). Damaged nerves do not transmit proper signals, resulting in a loss of sensation, hypersensation, or pain.
Macrovascular disease	Large blood vessels	Macrovascular disease refers to changes in the medium to large-size blood vessels. The blood vessel walls thicken and become hard and non-elastic (arteriosclerosis). Blood vessels also become clogged with mounds of plaque (atherosclerosis). Eventually, the flow of blood may be blocked. This may lead to coronary heart disease; cerebral vascular disease; peripheral vascular disease (see below).

• *Peripheral vascular disease*	Blood vessels of legs and feet	Peripheral vascular disease refers to diseased blood vessels that supply the legs and feet. If blood flow is only partially interrupted, cramps, weakness, or pain in the legs when walking (claudication) may result. A completely blocked artery will cause severe pain and the leg will become cold and pale. Treatments include replacing the diseased artery surgically or opening the blood vessel by compressing plaque against the artery wall (angioplasty).
• *Coronary artery disease*	Heart	Coronary artery disease refers to diseased heart arteries. Cramping and angina may occur when blood flow is decreased. Complete blockage of an artery results in myocardial infarction (heart attack). Symptoms of angina and heart attack include chest pressure, cramping, heavy feeling in the chest, shortness of breath, and extreme fatigue. Treatments include coronary bypass surgery and angioplasty.
• *Cerebral vascular disease*	Heart	Cerebral vascular disease refers to diseased arteries in the brain. Partial blockage may result in temporary reductions of blood supply to a part of the brain (transient ischemic attacks). A complete loss of blood supply to an area of the brain due to clogging or breaking of a blood vessel results in a cerebral vascular accident (stroke). Symptoms include lightheadedness, dizziness, loss of ability to speak, slurred speech, confusion, and inappropriate behaviour.
Foot problems	Feet	Ulcers of the legs and feet occur in people with diabetes due to the combination neuropathy and peripheral vascular disease. Neuropathy causes a loss of sensation, so that foot injuries may go untreated and become infected. Decreased circulation to the feet and legs slows healing. Proper nourishment does not reach damaged tissue, and infected material is not destroyed. Even a small injury may progress to an ulcer. If the ulcer becomes infected this can lead to amputation.

In some people with Type 2 diabetes such diet and exercise changes will be enough to control their blood glucose levels and negate their diabetes. However, some people need additional help in the form of prescribed oral drugs. There are five classes of oral medicines licensed for use in the UK for the treatment of hyperglycaemia in Type 2 diabetes: Metformin; Sulphonylureas; Meglitinides; Glitazones; and Acarbose (ABPI, 2005). Each class works in a different way and may be prescribed individually or in combination, depending on what works best for the sufferer. Metformin is most commonly the first line of treatment and works by inhibiting the production of glucose in liver. Sulphanylureas and Meglitinides both work by binding to receptors on the ß-cells and stimulating them to produce more insulin, although they act on different receptors. The Glitazones class of drug are known as 'insulin sensitisers' and work by effecting the nucleus of fat, liver, and muscle cells (the main target cells of insulin), enhancing their sensitivity to the action of insulin. Finally, Acarbose inhibits the alpha glucosidase enzyme which breaks down complex carbohydrates into simple sugars such as glucose, and therefore reduces the blood glucose peak which follows a meal. If a person with Type 2 diabetes cannot achieve satisfactory control of their blood glucose with oral agents, they will be treated with insulin, normally in association with Metformin or a Sulphonylurea (ABPI, 2005).

Evidence from studies and trials suggest that the importance of maintaining good control of both blood glucose and blood pressure cannot be overstated. For instance, the intensive treatment of Type 1 diabetes and maintenance of tight blood glucose and blood pressure control has been shown to reduce the risk of developing new retinopathy

(eye disease) by 76% and reduce the risk of further worsening an existing eye condition by 54% (Diabetes Control and Complications Trial Research Group, 1993). Similarly, good blood glucose control has been observed to reduce the risk of retinopathy in people with Type 2 diabetes by 33% (UK Prospective Diabetes Study Group, 1998b). The risk of early and serious nephropathy (kidney disease) was also reduced by 54% and 33% (respectively) in persons with tight control of their Type 1 diabetes (Diabetes Control and Complications Trial Research Group, 1993), and improved blood glucose control was associated with a 33% decrease in risk of nephropathy for people with Type 2 diabetes (UK Prospective Diabetes Study Group, 1998b). Finally tight control of hypertension also reduced the risk of heart disease by 56% and stroke by 44% in people with Type 2 diabetes (UK Prospective Diabetes Study Group, 1998d, , 1998a, , 1998c).

Blood glucose and blood pressure are therefore important parameters in the management of diabetes and are monitored regularly by clinicians. Tests of glycosylated haemoglobin, most commonly the haemoglobin A1c (HbA_{1c}), are particular useful to clinicians as they provide a clear indication of blood glucose control over the 2-3 month period before the test. In the blood, glucose binds irreversibly to haemoglobin molecules within red blood cells. The amount of glucose that is bound to haemoglobin is directly linked to the concentration of glucose in the blood. Since red blood cells have a lifespan of approximately 90 days, measuring the amount of glucose bound to haemoglobin can provide an assessment of average blood glucose control during the 60 to 90 days prior to the test. Individual targets for HbA_{1c} are set by the clinician, but is normally set in the range of 6.5 - 7.5%. Using regular HbA_{1c} tests

(usually between 2-6 tests a year), a clinician is then able to assess how well a person has managed to control their blood glucose and whether they have managed to hit their target in between clinics. Any greater efforts on behalf of the person to improve control just before clinic attendance will not mask the underlying trend. If individual targets are not being met, the clinician can then change the treatment regimes to better suit the patient.

In addition to the monitoring done in clinics, it is also important to monitor on a daily basis as blood glucose may reach dangerously high (hyperglycaemic) or dangerously low (hypoglycaemic) levels depending on food intake, exercise, infection or medication. Daily self-monitoring can be achieved either by urine glucose testing or by blood glucose testing. The simplest method is urine testing, whereby a reagent strip is placed in the urine stream, and it changes colour to indicate the presence of glucose in the urine. The test is normally carried out before breakfast and before an evening meal (Campbell & Song, 2004). Although easy to conduct, the urine test has significant drawbacks: the relationship of urine glucose to blood glucose is unreliable - a clear positive result will only normally be achieved when blood glucose is in excess of 10.0 mmol L^{-1}, and urine strips can not detect hypoglycaemia. Urine analysis is therefore normally recommended for non-insulin dependent diabetes patient with greater control and for people who find blood testing difficult.

The alternative method is to test a sample of capillary blood taken by pricking the end of a finger with a lancet or needle. A spot of blood is then placed on a reagent strip. The reagent strip will either change colour (to be read manually or by a meter) or the

result will be read by electrochemical means in a meter (ABPI, 2005). The results of blood glucose monitoring are far more accurate and reliable than those achieved by urine glucose monitoring and can also indicate low levels of blood sugar, and thus they provide warning of hypoglycaemia. For this reason, regular blood testing is recommended to all insulin treated diabetes patients and is encouraged for some non-insulin dependent diabetes patients who are struggling to control their diabetes. People with Type 1 and 2 insulin dependent diabetes should test their blood glucose before and after meals and before bed-time (European Diabetes Policy Group, 1999b). Orally medicated or diet controlled Type 2 diabetes patients who test their blood should do so once or twice either before or after a meal.

The European Diabetes Policy Group (1999a) suggest that all people with diabetes should be encouraged to do some kind of testing for the following benefits:

- *Education on effects of diet and physical activity on blood glucose;*
- *Assurance of satisfactory blood glucose control;*
- *Coping with illness and new situations;*
- *Insulin dose adjustment and hypoglycaemia management where relevant.*

However, recently there has been debate within the NHS and the academic community as to whether, given the increasing availability of the HbA_{1c}, self-monitoring by people with diet or oral control diabetes is desirable or cost-effective (Bandolier, 2005a; NHS National Prescribing Centre, 2002). Urine glucose testing is the most popular form of self-monitoring for oral tablet and diet treated diabetes patients but is increasingly

being seen as a *"waste of time"* amongst clinicians, given the limitations of urine monitoring, the cost associated with it and the lack of evidence of improved glycaemic control (Bandolier, 2005b). Therefore many new patients who would previously have been encouraged to urine monitor are no longer asked to test their urine glucose and instead are monitored by general practitioners and clinician using HbA_{1c} or blood glucose testing if necessary. However many older patients still self-monitor regardless and presumably find monitoring beneficial. Evans, Newton, Ruta, MacDonald, Stevenson, & Morris (1999) have found that uptake of strips for self-monitoring is lower in patients who live in deprived areas of Tayside.

2.5 Conclusions

The disease processes which result in Type 1 and Type 2 diabetes are still poorly understood. The exact auto-immune processes that result in Type 1 diabetes remain elusive, and very little is known regarding the actual physiological pathways which lead to Type 2 diabetes. What is known is that both Types of diabetes occur in people who are genetically susceptible and who are exposed to environmental risk factors. Viral infections and ingestion of certain dietary compounds (such as cows' milk and nitrate/nitrite) are most commonly associated with Type 1 diabetes. Meanwhile, behavioural factors (such as obesity and lack of physical exercise) have clearly been implicated in the development of Type 2 diabetes. The different aetiologies of the two Types of the condition (i.e. the different genetic causes, disease processes and risk factors) result in very different geographical distributions at the international, national

and local level, which will be explored in Chapter 3. In addition, careful control of blood glucose helps to avoid diabetic complications, and self-monitoring may help blood glucose management as well as providing other benefits. A previous study has shown that there are significant socio-economic variations in the uptake of self-monitoring strips.

CHAPTER 3 - GEOGRAPHY OF DIABETES MELLITUS

3.1 Introduction

Both Type 1 and Type 2 diabetes have distinct and contrasting geographies, reflecting the differing aetiological pathways of the conditions. These differences can be observed in the incidence/prevalence of the conditions at the international, sub-national and small area level. Many international studies do not differentiate between Type 1 and Type 2 diabetes and so in the main reflect the incidence of Type 2 diabetes which is more common. However, at the small area level, more studies have focused on the geography of Type 1 diabetes. This reflects the uncertainty of which environmental factors are involved in the genesis of Type 1 diabetes, whereas powerful behavioural risk factors have been identified in the pathogenesis of Type 2 diabetes. In general, studies of Type 2 diabetes have concentrated on the characteristics of the individuals involved rather than investigating the area- or place-based characteristics which may lead to the condition.

3.2 Geography of Type 1 diabetes

Many of the studies that consider the geographic distribution of Type 1 diabetes focus on children. This is to help distinguish more clearly between people with Type 1 diabetes and Type 2 diabetes, given that most people with Type 1 diabetes are

diagnosed in childhood or early adulthood whereas most people with Type 2 diabetes are diagnosed later in life. However with the increased incidence of Type 2 diabetes in children and young adults there is still some potential for misclassification (Lobstein & Leach, 2004).

3.2.1 International variations in Type 1 diabetes incidence

Figure 3.1 shows the reported national incidence of childhood Type 1 diabetes worldwide. The condition is more common in countries of northerly latitudes and is particularly high in Northern Europe and North America. The southern hemisphere and eastern countries tend to have a lower reported incidence, with the exception of Australia and New Zealand. Much of the populace of North America and the Antipodean nations are of European descent and are of similar genetic stock, which may explain the high incidence of Type 1 diabetes. However, these countries also share similar westernised lifestyles.

Of the known risk factors for Type 1 diabetes, the consumption of cows' milk is higher in westernised countries. Scandinavian nations are also thought to have higher dietary N-nitroso compounds through their consumption of meat and smoked products (see section 2.2.4.3b). The temperate and cold climates of the more northerly latitudes may also provide more suitable conditions for viruses and other pathogens which could be related to the development of Type 1 diabetes (see section 2.2.4.3a).

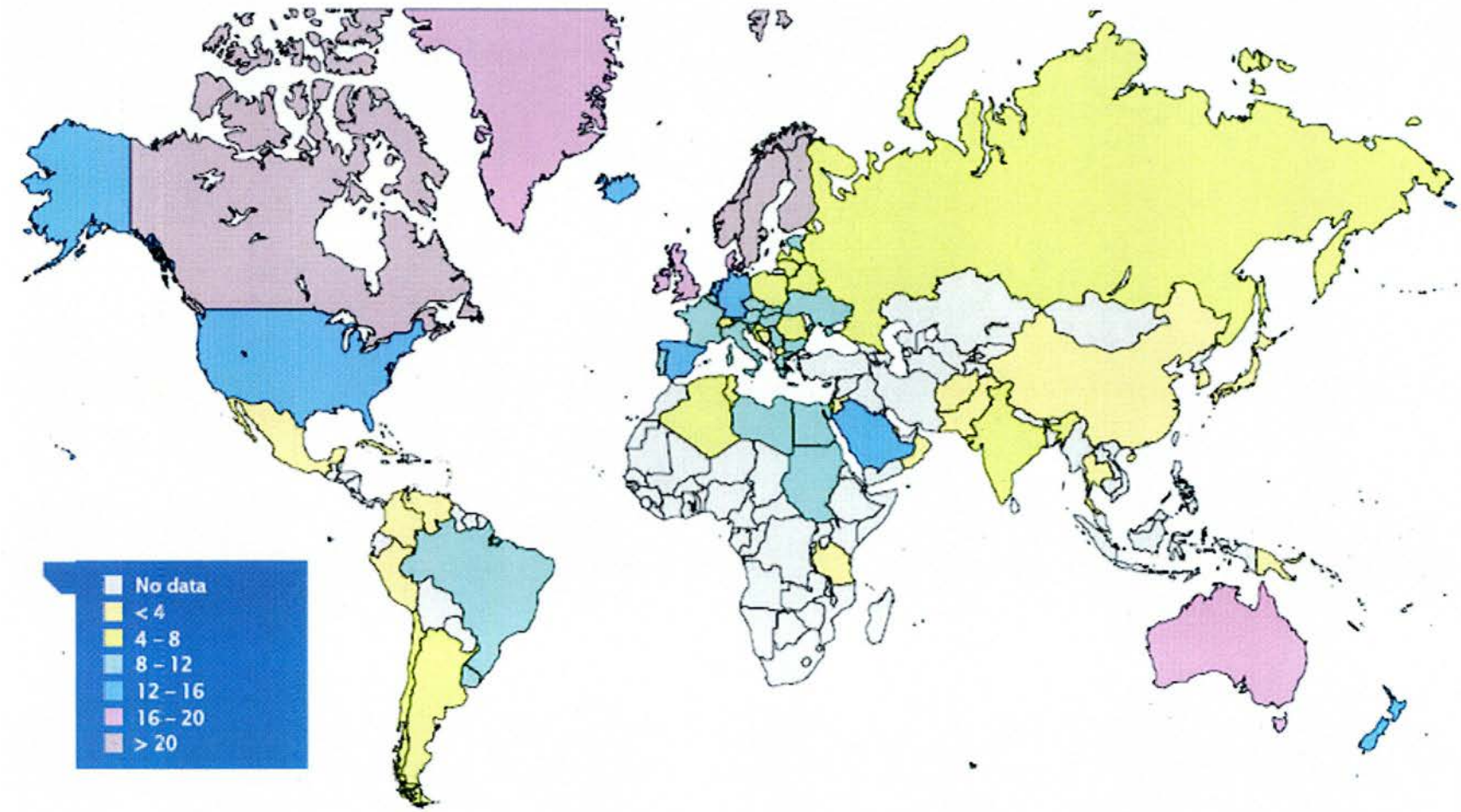


Figure 3.1 Published incidence rates of Type 1 diabetes (cases per 100,000 population per year) in children aged 0-14 year old by country (taken from the International Diabetes Federation, 2003, p.118)

The Mediterranean island of Sardinia is also known to have high incidence of childhood diabetes. Songini, et al. (1998), analysing childhood diabetes data from the EURODIAB ACE register, calculated the incidence on the island to be 33.2 per 100,000 children (95% CI: 30.6%, 35.9%) between 1989-94. For all the nations where incidence was known, this rate was only lower than that of Finland. The genetic homogeneity of the Sardinian island population and relatively small geographical variation in childhood diabetes incidence across the island, suggests that the raised incidence may be the result of a genetically susceptible population being relatively recently exposed to a uniformly distributed aetiological factor. Some suspicion has fallen upon the nitrate content of the drinking water in Sardinia, although at present there is no evidence to support this hypothesis (Casu, Carlini, Contu, Bottazzo, & Songini, 2000).

Elsewhere Onkamo, Vaananen, Karvonen et al. (1999) reviewed 37 studies of changing Type 1 incidence in 27 countries between 1960 and 1996. The authors found that overall Type 1 incidence had risen by 3.0% per annum (95% CI: 2.6%, 3.3%) when the data from all the studies were pooled together. Only one study, in Colorado, USA, reported a decreasing incidence of -0.2%. All of the other reviewed studies reported increases in incidence with a study in Leicester, UK, reporting the highest increase of 9.5%. The changing incidence for each study population is shown in Figure 3.2 & Figure 3.3. In addition to showing clear rises in incidence worldwide, the authors also observed that many of the studies in countries with traditionally low incidence of Type 1 diabetes (e.g. Poland, Hungary, China, Peru, Algeria, Japan, and Hawaii) had

experienced some of the largest increases. Meanwhile, in many of the populations with traditionally high incidence (e.g. Finland, Sweden, Norway, Canada and Scotland) the increase was lower than average (see Figure 3.4).

Similar results were also found by the EURODIAB TIGER study of childhood Type 1 incidence in Europe. Green and Patterson (2001) have shown that the incidence of childhood Type 1 diabetes increased by 3.2% (95% CI: 2.7%, 3.7%) annually in Europe from 1989 to 1998. The greatest rate of increase was for children aged 0-4 years old who experienced a 4.8% (95%-CI: 3.8%, 5.9%) rise, while the incidence in the 5-9 age group rose by 3.7% (95%-CI: 2.9%, 4.5%). The 10-14 age group experienced the lowest rate of increase of 2.1% (95%-CI: 1.4%, 2.8%). They also observed that the traditionally high-risk areas of Sardinia and Northern Europe seem to have reached a plateau in incidence whereas Central Eastern Europe is experiencing a particularly rapid increase. In this study, the UK was categorised as part of Atlantic Europe along with Iceland. During the time period of the study Atlantic Europe saw a 3.9% (95%-CI: 2.7%, 5.1%) per annum increase in incidence.

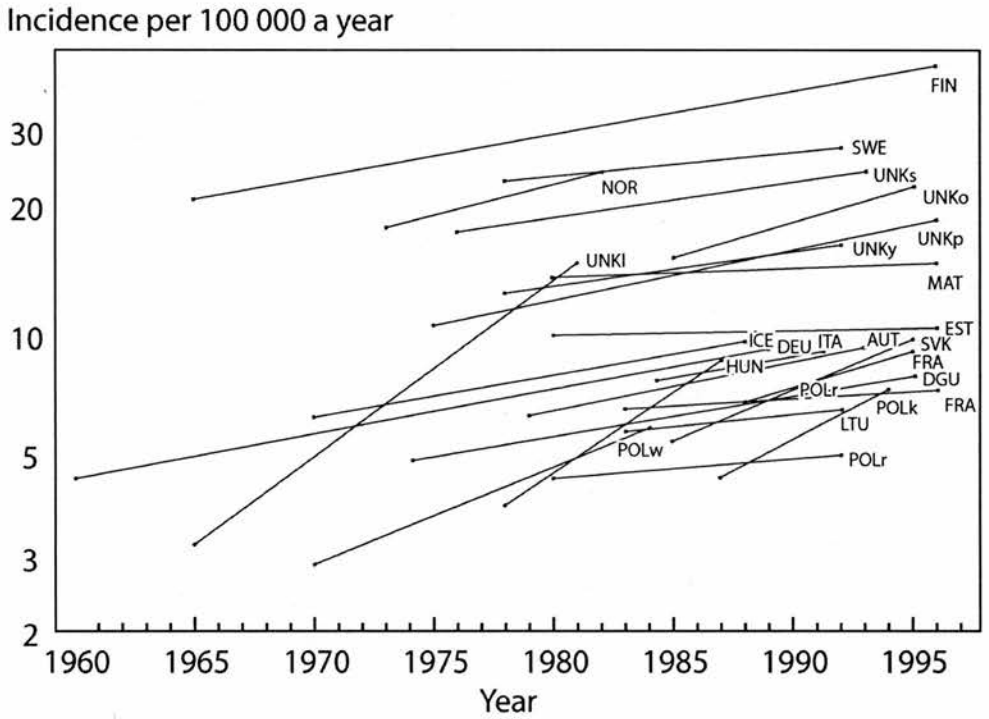


Figure 3.2 Trends in the incidence of Type 1 diabetes mellitus in European populations.

AUT: Austria; BGR: Bulgaria; DEU: East-Germany; EST: Estonia; FIN: Finland; FRA: France; HUN: Hungary; ICE: Iceland; ITA: Italy (Turin); LVA: Latvia; LTU: Lithuania; MAT: Malta; NOR: Norway; POLk: Poland (Krakow); POLr: Poland (Rzeszów); POLw: Poland (Wielkopolska); SVK: Slovakia; SWE: Sweden; UNKl (UK, Leicestershire); UNKo (Oxford); UNKp (Plymouth); UNKs (Scotland); UNKy (Yorkshire). Taken from Onkamo, Vaananen, Karvonen et al. (1999, p.1399).

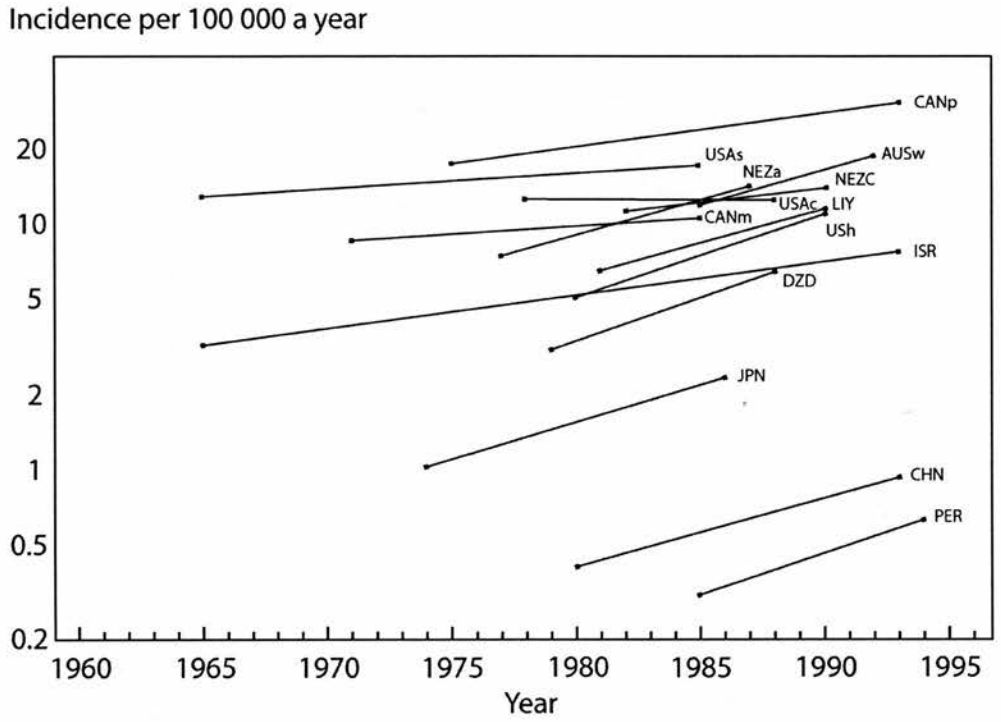


Figure 3.3 Trends in the incidence of Type 1 diabetes mellitus in Non-European populations.

DZD: Algeria (Oran); AUSw: Australia (West); CANm: Canada (Montreal); CANp: Canada (Prince Edward Island); CHN: China (Shanghai); ISR: Israel (Yemenite Jews); JPN: Japan (Hokkaido); LIY: Libya; NEZa: New Zealand (Auckland); NEZc: New Zealand (Canterbury); PER: Peru (Lima); USAa: USA (Allegheny County); USAc: USA (Colorado); USAh: USA (Hawaii). Taken from Onkamo, Vaananen, Karvonen et al. (1999, p.1399).

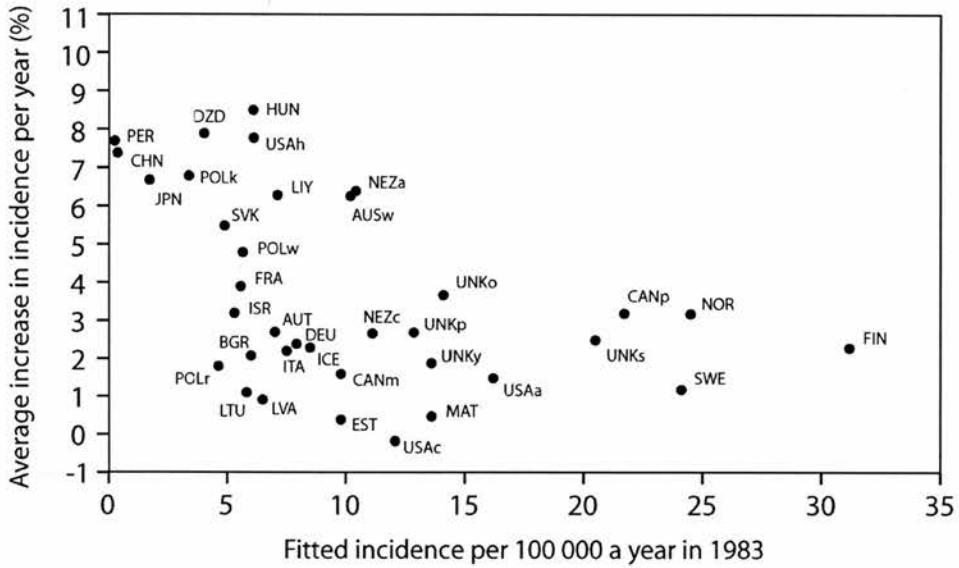


Figure 3.4 Association between the increase in incidence and the level of incidence of Type 1 diabetes.

Leicestershire, UK, has been excluded. DZD: Algeria (Oran); AUSw: Australia (West); AUT: Austria; BGR: Bulgaria; CANm: Canada (Montreal); CANp: Canada (Prince Edward Island); CHN: China (Shanghai); DEU: East-Germany; EST: Estonia; FIN: Finland; FRA: France; HUN: Hungary; ICE: Iceland; ISR: Israel (Yemenite Jews); ITA: Italy (Turin); JPN: Japan (Hokkaido); LVA: Latvia; LIY: Libya; LTU: Lithuania; MAT: Malta; NEZa: New Zealand (Auckland); NEZc: New Zealand (Canterbury); NOR: Norway; PER: Peru (Lima); POLk: Poland (Krakow); POLr: Poland (Rzeszów); POLw: Poland (Wielkopolska); SVK: Slovakia; SWE: Sweden; UNKo: UK (Oxford); UNKp: UK (Plymouth); UNKs: UK (Scotland); UNKy: UK (Yorkshire); USAa: USA (Allegheny County); USAh: USA (Hawaii); USAc: USA (Colorado). Taken from Onkamo, Vaananen, Karvonen et al. (1999, p.1400).

3.2.2 Geographical variations in Type 1 diabetes incidence in the UK

Comprehensive incidence data are provided for Scotland from a central register of childhood diabetes maintained by the Scottish Study Group for the Care of Diabetes in the Young. A study of childhood Type 1 diabetes based on the register data for 1984-93 suggested an incidence rate of 23.9 per 100,000 for children aged 0-14 years in Scotland (Rangasami, Greenwood, McSporran, Smail, Patterson, & Waugh, 1997). However, the national incidence rate is likely to have increased considerably since this study. More recent data from the register has been published in the form of standardised incidence rates by Scottish NHS Health Boards (Scottish Study Group for the Care of Diabetes in the Young, published in Scottish Diabetes Survey Monitoring Group, 2004). When this data is mapped (see Figure 3.5) it is clear to see that there is a latitudinal gradient as the incidence of diabetes increases northwards in Scotland.

Figure 3.5 shows that Glasgow Health Board has the lowest age-standardised incidence (22.1 per 100,000 children) of all the Health Boards and Orkney Health Board has the highest (39.1 per 100,000). The difference in incidence rates between Glasgow and Orkney suggests that the risk of developing childhood diabetes is 58% higher in Orkney. Tayside Health Board has one of the lowest incidences of childhood diabetes (23.5 per 100,000) with only Greater Glasgow, Dumfries & Galloway and the Borders having a lower incidence. Given the observable northward gradient in incidence, it can also be noted that Glasgow, Tayside and Grampian appear to have lower incidence than

one might expect. This may reflect lower Type 1 diabetes incidence in urban areas as these health boards are home to three of Scotland's largest cities (Glasgow, Dundee, and Aberdeen) and consequently have large urban populations. Higher incidence in rural and remote areas may potentially support the hygiene hypothesis (see section 2.2.4.4) as exposure to new pathogens, and the number of circulating pathogens, will probably be lower in rural populations than in urban populations.

Elsewhere in the UK, differences in the time periods of studies make direct comparisons difficult. A recently published study in North Wales has suggested that the incidence of childhood Type 1 diabetes had risen from 12.2 cases per 100,000 (95% CI: 9.2–16.1) to 31.3 (95% CI: 23.1–41.3) by 2002 (Harvey et al, 2005). However, due to the small number of cases, the confidence intervals around these estimates are relatively wide. In Northern Ireland, between 1989 and 2003, there were 1,433 new cases of Type 1 diabetes, giving a directly standardised incidence rate of 24.7 per 100,000 persons per year (Cardwell, 2006). Unfortunately, what is known about incidence in England is derived from a limited number of regional or metropolitan studies, many of which are now relatively old which limits their usefulness given the rate at which Type 1 diabetes is known to be rising (Karvonen, Tuomilehto, Libman et al., 1993; Onkamo, Vaananen, Karvonen et al., 1999).

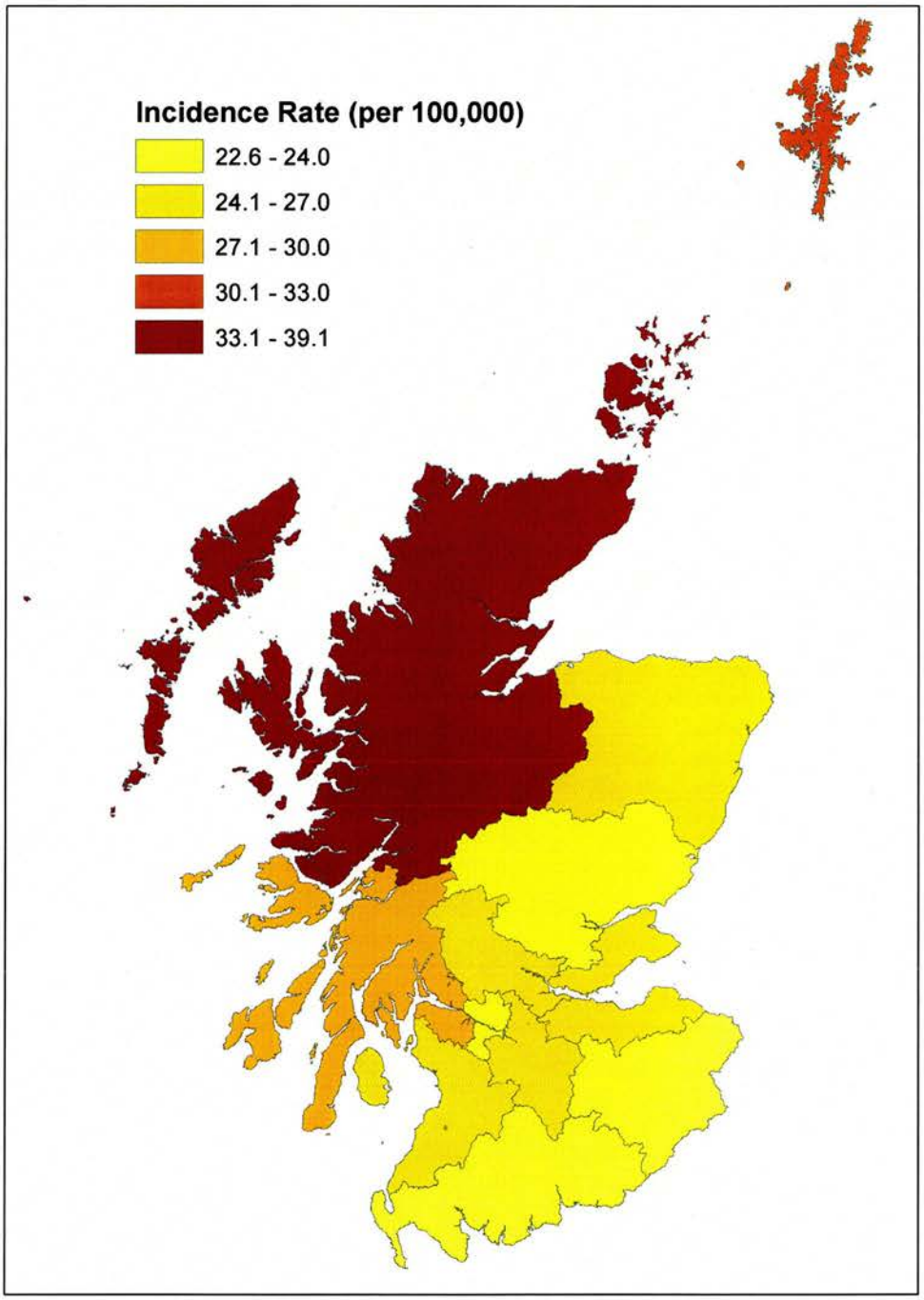


Figure 3.5 Age-standardised childhood Type 1 diabetes incidence rate per 100,000 children by Health Board in Scotland, 1984-2000 (Source: Scottish Study Group for the Care of Diabetes in the Young, published in Scottish Diabetes Survey Monitoring Group, 2004)

3.2.3 Small area variations in the incidence of Type 1 diabetes

Most UK studies of Type 1 diabetes incidence carried out in small areas (such as Census Wards in England & Wales and Census Area Statistic Sectors in Scotland) are concerned with identifying variations in suspected risk factors and whether they are associated with the incidence of diabetes. One such study conducted by Patterson and Waugh (1992) considered whether there were rural/urban differences in the incidence of childhood diabetes in Scotland. All the postcode sectors in Scotland were classified as rural, mixed or urban on the basis of the percentage of the sector designated as part of a built up area with a population greater than 500 (respectively <10%; 10-50%; >50%). Allowing for age and sex, the authors found incidence rates to be 20% higher in rural postcode sectors than in urban postcode sectors in Scotland. In contrast to the geography of many other illnesses, the lowest incidences of Type 1 diabetes were to be found in deprived urban areas. Similarly, a study in Yorkshire, UK, combined both small area Census data and data from water samples taken for the 148 water supply zones in the county to investigate the relationship between nitrate in drinking water and the incidence of childhood diabetes (Parslow, McKinney, Law et al., 1997). The study found a significant positive relationship between nitrate levels and diabetes incidence, after allowing for ethnicity, childhood population density, and Townsend deprivation score.

Meanwhile another study in Yorkshire has looked specifically at the geography of the condition across the county rather than modelling a specific relationship with suspected risk factors (McKinney, Law, Bodansky, Staines, & Williams, 1996). In the study the authors mapped age and sex standardised incidence ratios (SIRSs) of childhood diabetes at both the district and electoral ward level and found both to be geographically heterogeneous.

They ranged from 70 in Kirklees to 186 in Boothferry. Therefore the risk of developing diabetes was 30% lower in Kirklees than the Yorkshire average, whereas the risk was 86% higher in Boothferry. This also means that, after allowing for the age-sex structure, the children in Boothferry were 116% more likely to develop Type 1 diabetes than children in Kirklees. A visual inspection of the maps suggests that districts with higher population densities have a lower incidence of childhood Type 1 diabetes than districts with lower population densities. This heterogeneity of risk was also evident at the small area level as the electoral ward SIRs also varied markedly. Even districts with a low overall SIR often contained electoral wards with high SIRs. This heterogeneity of Type 1 risk in the electoral wards of Yorkshire may be partly explained as the result of random effects generated by the relatively small numbers of cases in small areas. However, it does appear that heavily populated urban electoral wards have lower incidence than the rural and semi-rural electoral wards.

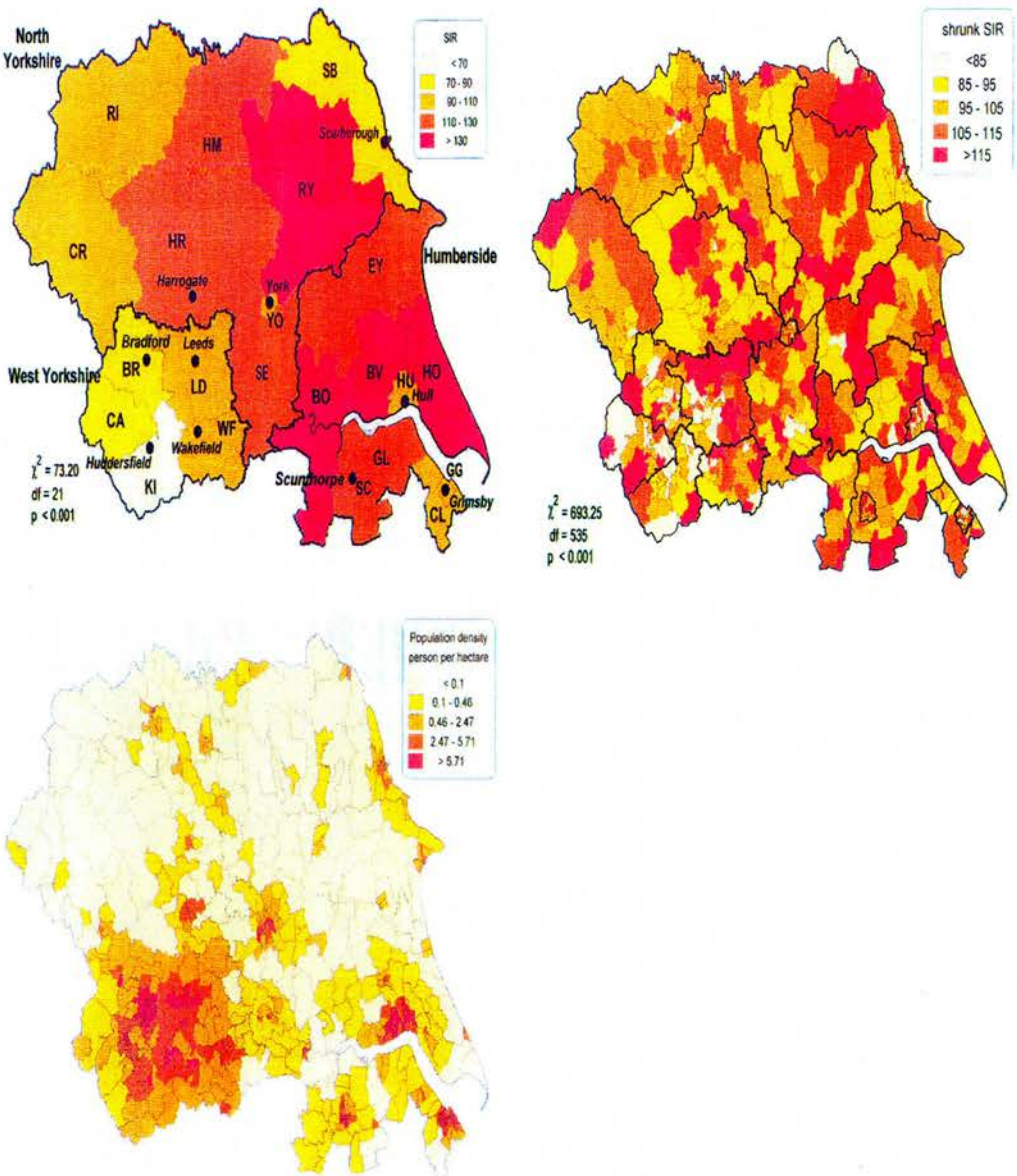


Figure 3.6 Childhood (0-14 years) Type 1 diabetes and population density in Yorkshire. (Taken from McKinney, Law, Bodansky et al., 1996). Top Left: Childhood Type 1 diabetes SIRs by district. Top right: Childhood Type 1 diabetes shrunk SIRS by electoral ward. Bottom: Childhood population density.

3.3 Geography of Type 2 diabetes

Studies of Type 2 diabetes are most often prevalence based rather than incidence based. There are probably many reasons for this, including the difficulties in defining when a person with Type 2 diabetes should be regarded as having been diagnosed, the lack of emphasis generally placed on the role of place on the aetiology of the condition, and the cost of collating incidence information given the large number of people who develop Type 2 diabetes. In addition, many people with Type 2 diabetes often remain undiagnosed (see section 2.3.1) and therefore the prevalence rates of diabetes will not only reflect the number of people with the condition in the population, but also the likelihood of presentation by an individual and the ability of health services to diagnose the condition. Therefore at the national level, prevalence rates of diabetes will be affected by social and cultural phenomena affecting health service utilisation as well as the accessibility of health services by various sections of the population. At the sub-national level, prevalence rates will similarly be affected by the utilisation of differing demographic, ethnic and socio-economic sub-groups, and by accessibility and different operating practices of primary and secondary health care centres and their practitioners (Brown, Ettner, Piette, Weinberger, Gregg, Shapiro et al., 2004; Edwards, Burns, McElduff, Young, & New, 2003; Goyder, McNally, & Botha, 2000).

3.3.1 International variations in diabetes prevalence

Figure 3.7 provides a map of the estimated diabetes prevalence worldwide. Although the map is not specific to Type 2 diabetes and will include other Types of diabetes, such as Type 1 and Type 3 (a rare form mostly commonly found in the Caribbean), Type 2 diabetes will account for the vast majority of these cases and the differences in geographic distribution. The affluent westernised and westernising countries have the highest prevalence of the condition and the relatively poor countries of Africa, South East Asia and South America have the lowest prevalence. North America, Eastern Europe, Russia, the richer countries of the Middle East, and Malaysia seem to have particularly high prevalence. In the global context, the 3.0% prevalence of diabetes in the UK is actually relatively low, which is perhaps surprising considering the UK as a nation has one of the highest percentages of the population classified as obese (approximately 25%) outside of the United States (International Diabetes Federation, 2003).

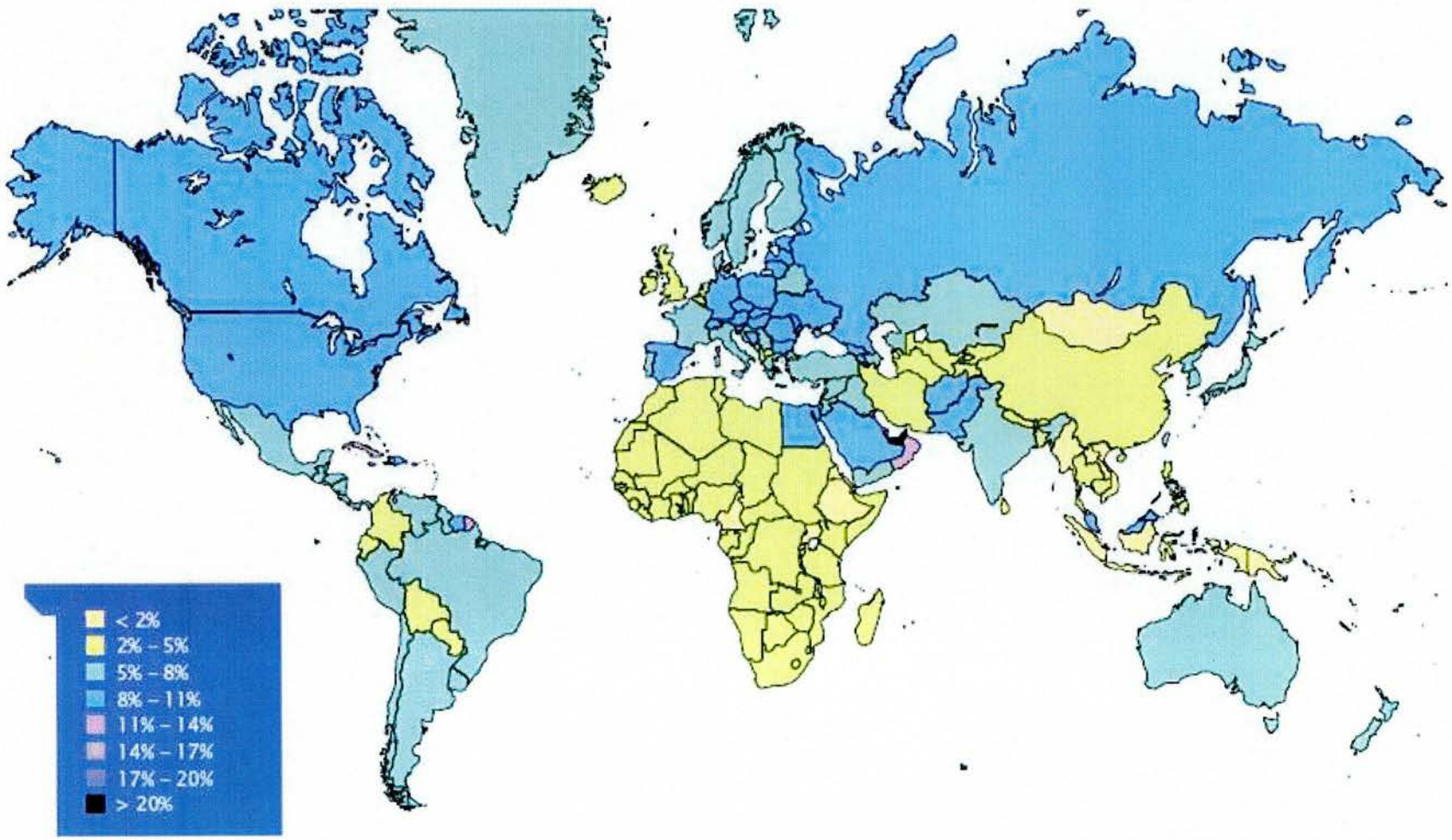


Figure 3.7 Estimated prevalence of diabetes by country (taken from the International Diabetes Federation, 2003, p.26)

3.3.2 UK variations in diabetes prevalence

At present there are no breakdowns of diabetes for the individual countries of the UK. Diabetes UK have published estimated numbers of diagnosed diabetes by country in 2004, but these calculations were primarily an interpolation of the UK prevalence rate at the time (2.6%) applied to the mid year population estimate of each country. As such, they estimated that there were 130,000 diagnosed diabetes patients in Scotland, 1,280,000 in England, 80,000 in Wales, and 40,000 in Northern Ireland. However as the estimates are based on the overall UK rate they can not be used to compare Type 2 prevalence between the nations.

At a regional level, age-standardised prevalence rates by the health boards in Scotland have been published as part of the 2003 Scottish Diabetes Survey (Scottish Diabetes Survey Monitoring Group, 2004), and are shown in Figure 3.8. The rates were highest in the more heavily populated and urbanised health boards in the central belt of Scotland, particularly in the east, and lowest in the more rural and remote areas of northern Scotland. The Tayside Health Board had a relatively high prevalence rate at 2.91%. One possible explanation for the high prevalence in Tayside may be that the health board serves the city of Dundee, which is one of the few large urban centres in Scotland, and contains some of the most deprived urban areas in Scotland outside Glasgow and Edinburgh (social status is strongly associated with increased prevalence of Type 2 diabetes, see section 2.3.2.5). However, part of the explanation could be that

ascertainment of Type 2 diabetes cases in Tayside is higher than in some of the other health boards. The Diabetes Audit and Research Tayside Scotland (DARTS) dataset was founded in 1996 to improve diabetes data collection and provide high quality data for research: in the process of collating and administering the dataset the ascertainment may well be better than found in other health boards (see section 4.3 for more information on DARTS).

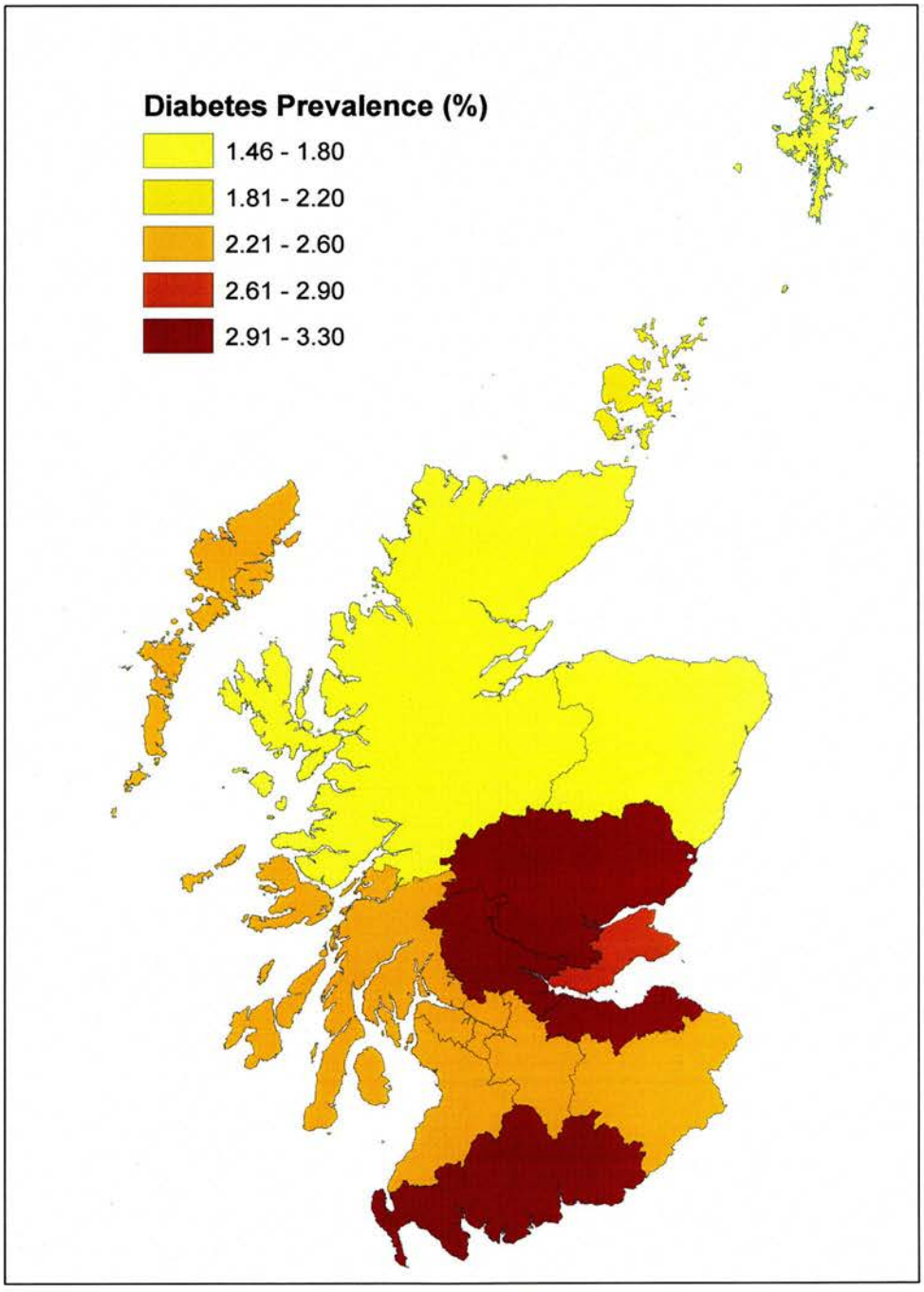
Given that developing Type 2 diabetes is strongly related to low social status it is perhaps surprising that the prevalence rate for Greater Glasgow, which contains the greatest concentration of deprivation in Scotland, was only marginally higher than the Scottish average of 2.52% at 2.57%, whereas Dumfries and Galloway (primarily a very rural area of Scotland) had the highest prevalence rate at 3.30%. At present, it is not clear how accurate the prevalence rates provided by the survey are. It is possible that the rates may be accurate and reflect genuine differences in the geographical distribution of Type 2 diabetes. However, the rates should probably be viewed with a certain amount of caution as they may, at least in part, also reflect differences in ascertainment depending on how diabetes data is collated in each health board.

For instance, it is possible that the reported prevalence in more remote areas of Scotland may be artificially low (or indeed artificially high), as these health boards may have fewer resources to collate and validate information on Type 2 diabetes sufferers in their population. This would seem to be borne out in the remainder of the Scottish Diabetes Survey (Scottish Diabetes Survey Monitoring Group, 2004) as many of the less populated health boards, such as Orkney, Shetland, and the Western Isles, have had

particular difficulty in providing other data on various characteristics of their diabetic populations (e.g. ethnicity, date of diagnosis, BMI, smoking status and diabetic complications). However, despite these potential problems the map shows the urban bias in the geographical distribution of Type 2 diabetes that one might expect considering the strong positive relationship known to exist between social status and diabetes (see section 2.3.2.5).

Elsewhere, Barker, Gardner, & Power (1982) are among the few authors who have considered the relationship between diabetes and socio-economic factors from a geographical perspective. In their study of nine British towns, they identified three groups of three towns of similar latitudes but with differing socio-economic conditions. In the north, the towns studied were York, Wakefield and Preston; in the central latitudes the towns were Chester, Derby, and Stoke; and in the south Ipswich, Plymouth and Newport. Data was then prospectively collected on diabetes incidence in people aged 18-50 years old. The incidence of Type 2 diabetes was considerably higher (23 per 100,000) in the three towns with 'worst' socio-economic conditions (Preston, Stoke, and Newport), than in the socio-economically 'intermediate' towns (13 per 100,000 overall for Wakefield, Derby and Plymouth) and the 'better' towns (10 per 100,00 overall for York, Chester and Ipswich). Barker, Gardner, & Power also considered there to be no relationship with latitude. Although incidence rose northwards in the towns of 'intermediate' and 'worse' socio-economic conditions, incidence was lower in the northern towns with 'better' socio-economic condition (see Table 3.1)

Table



3.1

Figure 3.8 Age standardised diabetes prevalence for NHS Health Boards in Scotland, 2003. Orkney data from 2001, Western Isles data from 2002. (Taken from Scottish Diabetes Survey Monitoring Group, 2004, p.14).

Latitude	Socio-economic conditions			All Conditions
	Better	Intermediate	Worse	
North	7 (York)	18 (Wakefield)	27 (Preston)	17
Central	8 (Chester)	10 (Derby)	22 (Stoke)	13
South	14 (Ipswich)	10 (Plymouth)	21 (Newport)	15
All latitudes	10	13	23	

Table 3.1 Average annual age-standardised incidence of Type 2 diabetes (per 100,000) in nine British towns, 1977-1979. Taken from Barker, Gardner, & Power (1982, p.423).

3.3.3 Small area variations in Type 2 diabetes prevalence

Those studies of Type 2 diabetes in small areas in the UK have tended to investigate the relationship between prevalence and one of a number of measures of socio-economic deprivation (Benach, Yasui, Borrell, Saez, & Pasarin, 2001; Connolly, Unwin, Sherriff et al., 2000; Evans, Newton, Ruta et al., 2000). Thus, Connolly, Unwin, Sherriff et al., (2000) investigated diabetes prevalence in Middlesbrough and East Cleveland, UK and found a significant relationship between Type 2 prevalence for men and women and the deprivation quintile of the electoral ward of residence. The prevalence of diabetes in the least deprived quintile was 13.4 per 1,000 for men (95% CI: 11.4–15.4) and 10.84

per 1,000 (95% CI: 9.0–12.7) for women. In contrast, the prevalence was higher for both men and women in the most deprived quintiles, with rates of 17.2 per 1,000 (95% CI: 15.5–19.0) and 15.5 per 1,000 (95% CI: 13.8–17.1) respectively.

Evans, Newton, Ruta et al. (2000) conducted a similar study in Tayside, in which they calculated the odds ratios of having Type 2 diabetes, adjusted for age, based on the Carstairs deprivation category (or 'depcat') of the postcode sector of residence. The study consisted of 5,474 people with Type 2 diabetes recorded in the DARTS dataset as being resident in Tayside in January 1993. Those in deprivation categories 6 and 7 (the most deprived) were 1.6 times (95% CI: 1.4–1.8) more likely to have diabetes compared to those in deprivation category 1 (least deprived): see Table 3.2.

Deprivation Category	Total (n)	Adjusted odds ratio	95% confidence intervals
1 (least deprived)	366	-	-
2	930	1.07	(0.95-1.21)
3	1346	1.11	(0.99-1.25)
4	1123	1.34	(1.19-1.52)
5	607	1.27	(1.11-1.45)
6 and 7 (most deprived)	1102	1.61	(1.43-1.82)

Table 3.2 Adjusted odds ratios for Type 2 diabetes prevalence by Carstairs deprivation category in Tayside, January 1993 (taken from Evans, Newton, Ruta et al., 2000).

Finally, Bhopal, Hayes, White et al. (2002) have compared the relationships between a number of measures of social status and the prevalence of glucose intolerance in European and South Asian Populations in Newcastle, UK. They found positive relationships between glucose intolerance and social class, educational attainment and Townsend Deprivation Index for both European and South Asian ethnic groups. However, the positive relationships found between glucose intolerance and the various measures of social status were only statistically significant ($p<0.05$) in the European population, and were not significant in the various South Asian ethnic groups.

3.3.4 Conclusions

Internationally, Type 1 diabetes is highest in Caucasoid populations and increases with latitude, perhaps reflecting geographical variations in genetic susceptibility and environmental risk factors such as viral infections, nitrate/nitrite content in food and drinking water, and consumption of cow's milk. Within Scotland, Type 1 diabetes incidence is up to 58% higher in the rural and remote regions than in the most populated regions. This Scottish rural bias may also be related to the environmental risk factors associated with higher latitudes, as the rural areas of Scotland (e.g. the Highlands, the Western Isles, Orkney and Shetland) are typically in the north. However, it is also possible that the lower population densities in these areas are related to lower exposure to common pathogens with an ensuing increased risk of autoimmune disease as proposed by the hygiene hypothesis.

Type 1 diabetes is increasing both worldwide and across Europe. However, it is interesting to note that major international studies suggest that some of the largest increases of Type 1 diabetes are in populations with traditionally low incidence - e.g. Eastern Europe, China, Peru, Algeria, Japan, and Hawaii (Green & Patterson, 2001; Onkamo, Vaananen, Karvonen et al., 1999). This may be caused by environmental factors, previously associated with nations of high incidence, becoming more prevalent in previously low incidence countries. It is perhaps no coincidence that of the countries listed above, most of them have become less internationally or culturally isolated over recent decades. It is not known what environmental factors have led to these increases in incidence, but some conjecture could be given to dietary changes, increased exposure to diabetogenic pathogens, or to the spread of increased hygienic practices.

Meanwhile, Type 2 diabetes in the global context seems to be associated with affluent westernised and westernising countries. However, if this association is true, prevalence seems to be lower than might be expected in Western Europe and the UK. With the predicted future spread of westernised lifestyles, with their propensity towards obesity and other diabetogenic risk factors, the prevalence of diabetes is expected to double between 2000 and 2030 (Wild, Roglic, Green et al., 2004). Within the UK and other developed nations, Type 2 diabetes is more prevalent in deprived urban areas and among the poorer people in these affluent societies (Agardh, Ahlbom, Andersson, Efendic, Grill, Hallqvist et al., 2004; Brancati, Whelton, Kuller, & Klag, 1996; Chaturvedi, Jarrett, Shipley, & Fuller, 1998; Kumari, Head, & Marmot, 2004; Larranaga, Arteagoitia, Rodriguez, Gonzalez, Esnaola, & Pinies, 2005; Robbins, Vaccarino, Zhang, & Kasl, 2005; Tang, Chen, & Krewski, 2003).

At the small area level in the UK, much of what is known about Type 2 diabetes is garnered from cross-sectional prevalence studies (Connolly, Unwin, Sherriff et al., 2000; Evans, Newton, Ruta et al., 2000; Meadows, 1995), which detail the relationship between diabetes prevalence and socio-economic deprivation at a specific moment in time. However none of these studies map the geographic distribution of diabetes prevalence within small areas, but rather consider the relationship between diabetes and socio-economic deprivation by aggregating small areas into deprivation quintiles or categories. This, in many ways, reflects the a-spatial nature in which the aetiology of Type 2 has tended to be considered in the past. These studies of diabetes that have included area deprivation scores have tended to treat these characteristics as surrogates for individual-level lifestyle risk factors, such as diet, exercise, weight, and smoking status, for which data are usually not available. Thus, these deprivation scores are not assumed to reflect the characteristics of areas or places.

Interpreting the observed relationships between diabetes prevalence and socio-economic deprivation is problematic because the place in which a person resides at the time of a particular study (their 'prevalent position') may not be the place they were first diagnosed with the condition (their 'incident position') or indeed the place(s) where they were exposed to the diabetogenic factors which resulted in disease onset later in life. Therefore, an alternative explanation for the observed relationship between diabetes prevalence and deprivation might be the result of health selective migration. Longitudinal studies have shown that the relationship between deprivation and a variety of health outcomes may change over time because of health-selective (im)mobility

(Boyle, Norman, & Rees, 2002; Brimblecombe, Dorling, & Shaw, 1999; Norman, Boyle, & Rees, 2005). In this model, people with diabetes have greater difficulty gaining and maintaining employment (Robinson, Yateman, Protopapa, & Bush, 1990) and therefore may well move to cheaper accommodation in more deprived areas or be unable to afford to move out of deprived areas.

CHAPTER 4 – DEPRIVATION AND DIABETES MELLITUS IN TAYSIDE

4.1 Tayside

Tayside is one of fourteen health boards in Scotland[1]. In this thesis, any mention of Tayside refers to the area covered by the Tayside Health Board, unless specifically stated otherwise. Health boards are responsible for the provision of primary and secondary health care service, and community and mental health provision. This is achieved by contract services, such as General Practices and NHS Dentists, and direct management of others such as hospitals. The Tayside Health Board is located on the east coast of Scotland, north of the heavily populated 'central belt' of Scotland, sandwiched between the Highland and Grampian Health Boards to the north and the Forth Valley and Fife Health Boards to the south (Figure 4.1). Tayside covers an area of 7,640km^2 and was recorded as having a population of 389,012 (Males, 186,770; Females, 202,242) in the 2001 Census of Population. The Grampian Mountains bisect Tayside from the south east to the northwest (Figure 4.2), the lower reaches of the mountain range dominate the north western half of the Tayside Health Board. As a consequence, the north-west of Tayside is sparsely populated and the northern border part of Tayside is relatively remote.

[1] As of April 2006 the Clyde and Argyll Health Board has become defunct and its area split between the Highlands and Greater Glasgow Health Boards. Note that digital boundary files have not been released encompassing the change and therefore all maps will include Clyde and Argyll Health Board.

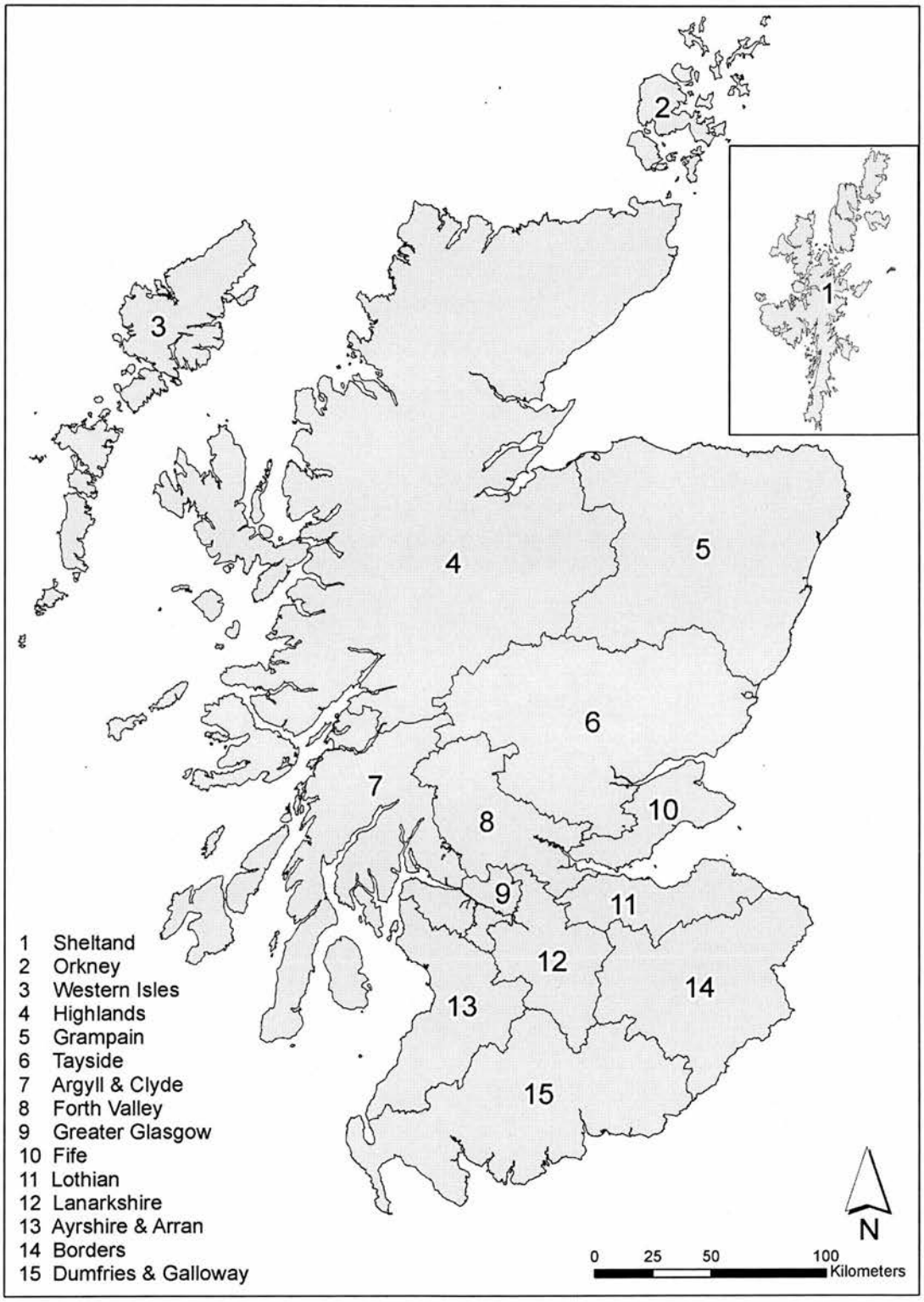


Figure 4.1 NHS Scotland Health Boards in 2001. Tayside Health Board is labelled as '6'. (Created using boundaries from UK Borders).

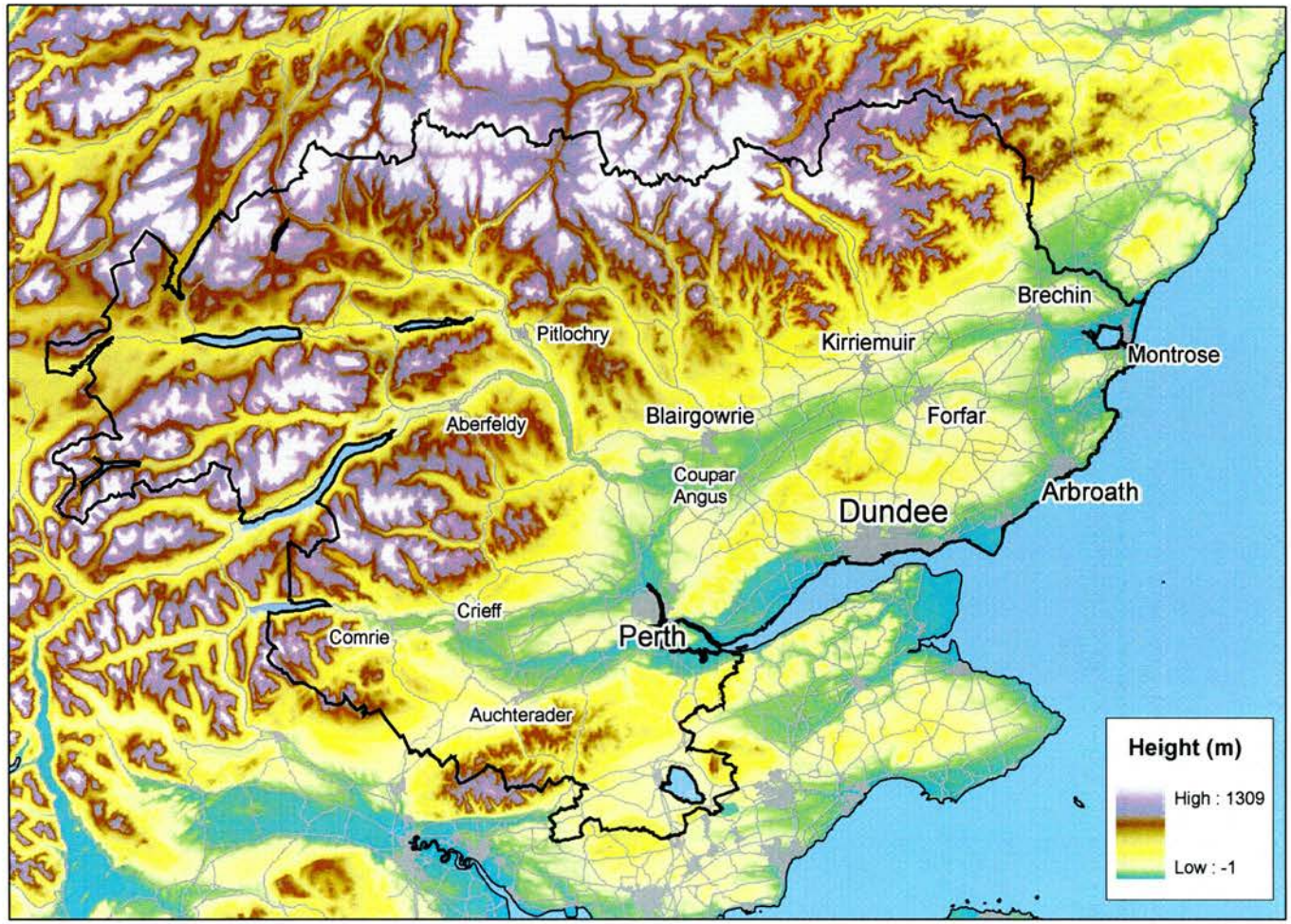


Figure 4.2 Relief map of Tayside also showing roads and major settlements. Digital boundaries from UK Borders, Digital Elevation Model courtesy of Digimap, © Crown Copyright/database right 2006. An Ordnance Survey/(Datacentre) supplied service.

The lower-lying south-west half of Tayside is comprised mainly of rural farmland and farming communities. This rural landscape is punctuated by historic market and county towns such as Forfar and Perth, while along the coast are the fishing ports of Montrose and Arbroath.

The port city of Dundee lies in the south of Tayside and is the region's major urban centre and Scotland's fourth largest city. Dundee is known for its industrial past, and was particularly famous for 'jute, jam and journalism', although these traditional industries (and many of the industries that supplanted them) have now all but disappeared (Whatley, 1992). In the post-industrial era, Dundee has struggled to find mass employment for its population, and as a result suffered de-population during the late 1980's (Dundee City Council, 2000). The city has recently found a niche in high-technology and health-based industries, such as video game production and biomedical research, taking advantage of the known strengths of Dundee and Abertay Universities. However, these industries still only employ a small proportion of the workforce and unemployment in Dundee is still relatively high at 4.4% compared to the 3.2% Scottish average (Scottish Economic Research, 2006). The city is also home to some of the most concentrated areas of deprivation in Scotland (see section 4.2). Unlike other industrial cities in the UK, Dundee is not ethnically diverse with only 3.7% of the population recorded as non-white in the 2001 Census (1.9% of the Tayside population was non-white).

4.2 Deprivation

Deprivation is an important concept in many facets of social research and has had an important role in the epistemology of social inequality in both academic and political spheres. To most researchers deprivation has intuitive meaning, allowing them to identify 'deprived' people or places, based on their personal perceptions and preconceptions of society. Yet actually defining what constitutes deprivation is a difficult process, made more complicated by the number of near synonyms (e.g. need, disadvantage, and underprivilege) and other closely related concepts (e.g. poverty and social exclusion). To further complicate matters, deprivation is often employed as part of a compound term (e.g. 'social deprivation', 'material deprivation' or 'multiple deprivation') which is necessarily vague in order that it might have relevance to a wide range of socio-economic and health outcomes (Coombes, Raybould, Wong, & Openshaw, 1995).

Most definitions of deprivation in the British academic context are informed, at least in part, by the work of Townsend, who described deprivation as a negative state whereby a person has reduced ability to participate:

> *"in the activities and* [do not] *have the living conditions and amenities which are customary, or at least widely encouraged or approved in the societies to which they belong"* (Townsend, 1979, p.31).

From this definition, deprivation can be further split according to its material and social elements. Material deprivation refers to the lack of, or lack of access to, material resources and this notion is intimately linked to the sociological concept of relative poverty. People living in poverty are highly likely to experience material deprivation. However, it is conceivable for material deprivation to exist independent of poverty, and social structures and processes relating to age, gender, race and social class may also modify one's access to key resources (e.g. education, employment, or healthcare) independent of income or material wealth. This social deprivation creates barriers to social resources and functions, limiting the individuals' ability to take a full and active role in society. For example, Townsend defines social deprivation as:

> *"the non-participation in the roles, relationships, customs, functions, rights and responsibilities implied by membership of a society and its subgroups. People are socially isolated, withdrawn or excluded maybe due to racism, sexism, ageism... as well as more 'natural' outcomes of ageing, or life processes such as disablement or family bereavement."* (Townsend, Phillimore, & Beattie, 1988, p.37).

In recent years, with the increased focus on social exclusion, the debate has widened concerning which political, social, cultural, economic and demographic processes act to exclude people from full participation in society. Material deprivation and poverty are important aspects in social exclusion but are seen as outcome measures and therefore less important than the processes which cause such disadvantage. These 'excluding'

processes relate to citizenship, lack of power and social integration and are bound up with the location of the citizen and so are inherently spatial (Lee & Murie, 1999).

4.2.1 Deprivation indices

Deprivation indices are area-based measures which have been formulated to quantify material deprivation. These indices are compositional in nature, measuring the proportion of an area's population living in various states of deprivation. These proportions are then standardised and combined into an index score of overall deprivation. The variables chosen to form the index represent various aspects of deprivation and are often derived from Census data. The advantages of using data from the Census are that it provides relevant, comprehensive and consistent data for small areas throughout the whole of the UK. The drawbacks are that the data available are limited to a relatively narrow set of socio-economic circumstances that, in the main, reflect material conditions in the area. The variables tend to act as proxies for income, wealth, and housing condition, rather than wider aspects of social deprivation. Indeed, in many studies Census-based deprivation indices are used as proxies for individual income in the absence of such data.

The most commonly used deprivation scores in the Scottish context are the Carstairs Deprivation Index (Carstairs & Morris, 1991) and the Scottish Index of Multiple Deprivation (SIMD; Office of the Chief Statistician, 2004). The Carstairs Deprivation Index is derived from four Census variables. However, the SIMD is one of a newer

generation of deprivation indices which are designed to overcome the weaknesses of traditional Census-based deprivation measures through the inclusion of a broader set of variables. The measure is built on the premise that there are several types of deprivation, or deprivation domains, of which six can be explicitly measured: income; employment; health; education; housing and geographic access. These domains can also be regarded as operating in conjunction, providing a single summary measure of deprivation. A number of variables are used to calculate an index score for each domain. However rather than relying on Census data, these variables often come from other sources (mainly governmental), which allow the SIMD to be updated regularly. These domains are then weighted and combined to create an overall index of multiple deprivation, which encompasses the additive effects of deprivation in each domain.

Despite the SIMD being the preferred choice of deprivation measure, it was not possible to use the SIMD as the principal measure of deprivation in this study since SIMD data is not available for the very small Census output areas analysed in this thesis, and the SIMD is only available for 2004 and 2006. It does not cover the time periods (1985-1994; 1998-2001) of the diabetes data utilised in this thesis. Therefore the Carstairs Index of Deprivation has been employed as the principal measure of deprivation in this study, as the Index can be calculated for output areas for 1991 and 2001, and therefore is more directly comparable with the available diabetes data.

The Carstairs Deprivation Index combines four socio-economic variables which relate to different, though inter-related, aspects of deprivation: unemployment; overcrowding; non car ownership; and low social class (see Figure 4.3). Carstairs and Morris (1991)

contend that unemployment and being of low social class (i.e. being of semi-skilled or unskilled occupation) will reflect income and income potential and most likely reflect access to the job market. Car ownership is also thought to be a very good indicator of low income, as most families would want to own a car if they could possibly afford it. Car ownership also confers clear benefits regarding access to other material resources. Household overcrowding is likely to reflect poor living conditions and difficulty in accessing less overcrowded housing.

Carstairs Deprivation Index

1. *Unemployment* - unemployed male residents over 16 as a proportion of all economically active male residents aged over 16.
2. *Overcrowding* - persons in households with 1 and more persons per room as a proportion of all residents in households.
3. *Non car ownership* - residents in households with no car as a proportion of all residents in households.
4. *Low social class* - residents in households with an economically active head of household in social class IV (semi-skilled occupations) or V (unskilled occupations) as a proportion of all residents in households.

Figure 4.3 The variables which make up the Carstairs Deprivation Index (Carstairs & Morris, 1991)

The Carstairs Deprivation Index is a popular measure of deprivation specifically designed to be used in the Scottish context. The index is commonly employed in health studies to test for health inequalities (i.e. relationships between health outcomes and the socio-economic characteristics of an area). Indeed, having designed the Index,

Carstairs & Morris (1991) used their creation to analyse a range of health outcomes in their book 'Deprivation and Health in Scotland'. Since then the Index has been used to explore the socio-economic distribution of many conditions at the small area level, including: undernutrition and obesity in children (Armstrong, Dorosty, Reilly, & Emmett, 2003); cerebral palsy (Dolk, Pattenden, & Johnson, 2001); mental disorders and psychiatric admissions to hospital (Koppel & McGuffin, 1999; Weich, Twigg, Lewis, & Jones, 2005), and many others. The Carstairs Deprivation Index therefore is more than adequate for the requirements of this thesis.

4.2.2 Deprivation in Tayside

In 2001, the population of the Tayside Health Board was on average less deprived than the population of Scotland as a whole. The Carstairs Deprivation Index score for Tayside was -1.09 and the Index was standardised in such a way that the average deprivation for the whole of Scotland scored 0.00. Tayside Health Board was the 8th (out of 15) most deprived health board in Scotland. In comparison, Greater Glasgow Health Board had the highest Carstairs score of 3.70, and Grampian the lowest score of -3.73 (see Figure 4.4).

However, the 2001 Carstairs scores vary widely across smaller areas within Tayside. The largest concentrations of deprivation in Tayside were in the City of Dundee (see Figure 4.5) and in the other urban centres. Of the top 5% most deprived output areas in Scotland, five were in Tayside. One was in Dundee, two were in Perth and the

remainder were in Arbroath and Crieff. In general, the more rural areas of Tayside were ascribed as having low levels of deprivation using the Carstairs Index, although it is well-known that deprivation is a more difficult concept to measure in rural areas where, for example, car ownership is more of a necessity than a privilege (Haynes & Gale, 2000).

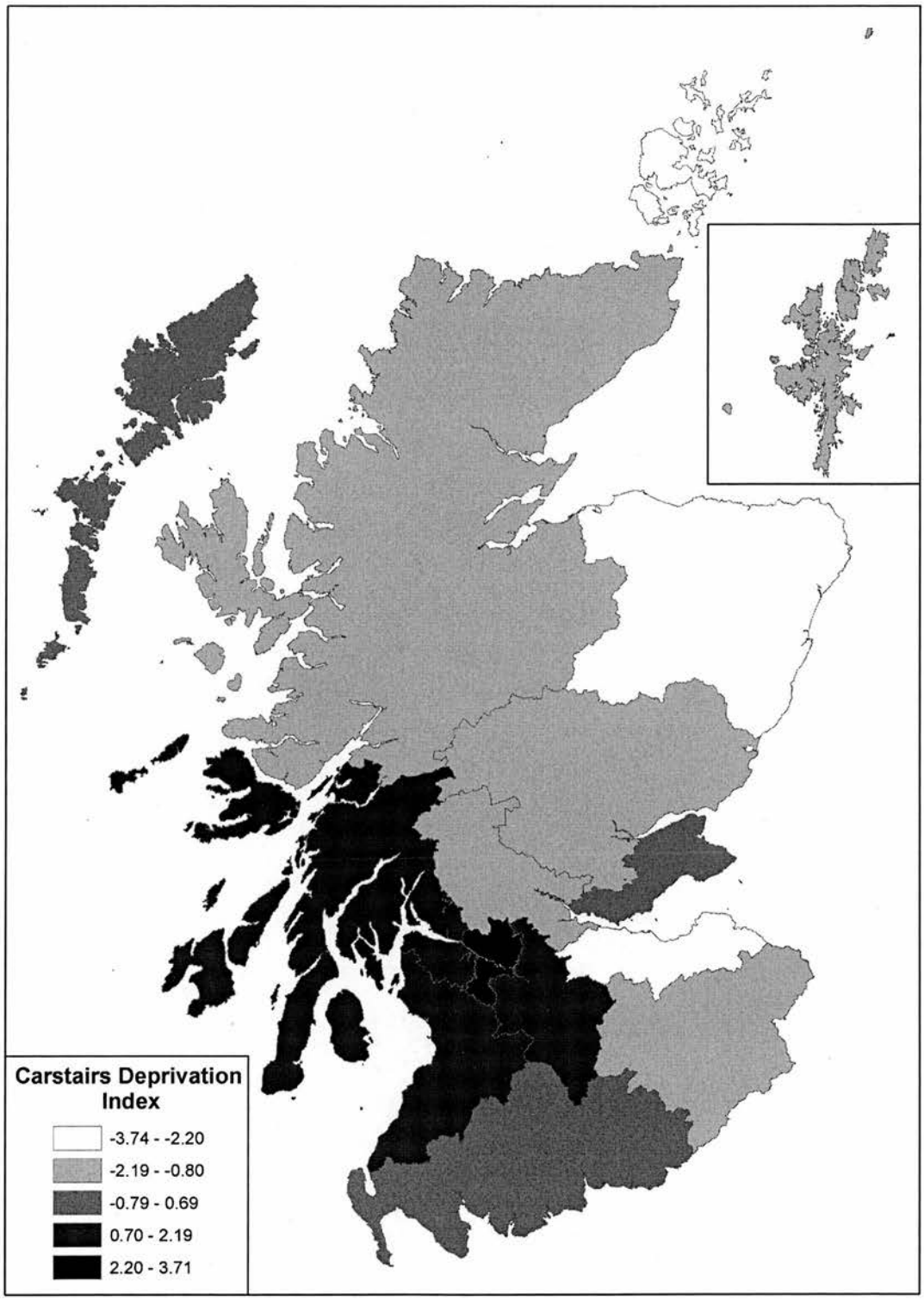


Figure 4.4 Carstairs Deprivation Index 2001 for Scottish NHS Health Boards (created using boundaries from UK Borders and 2001 Census data).

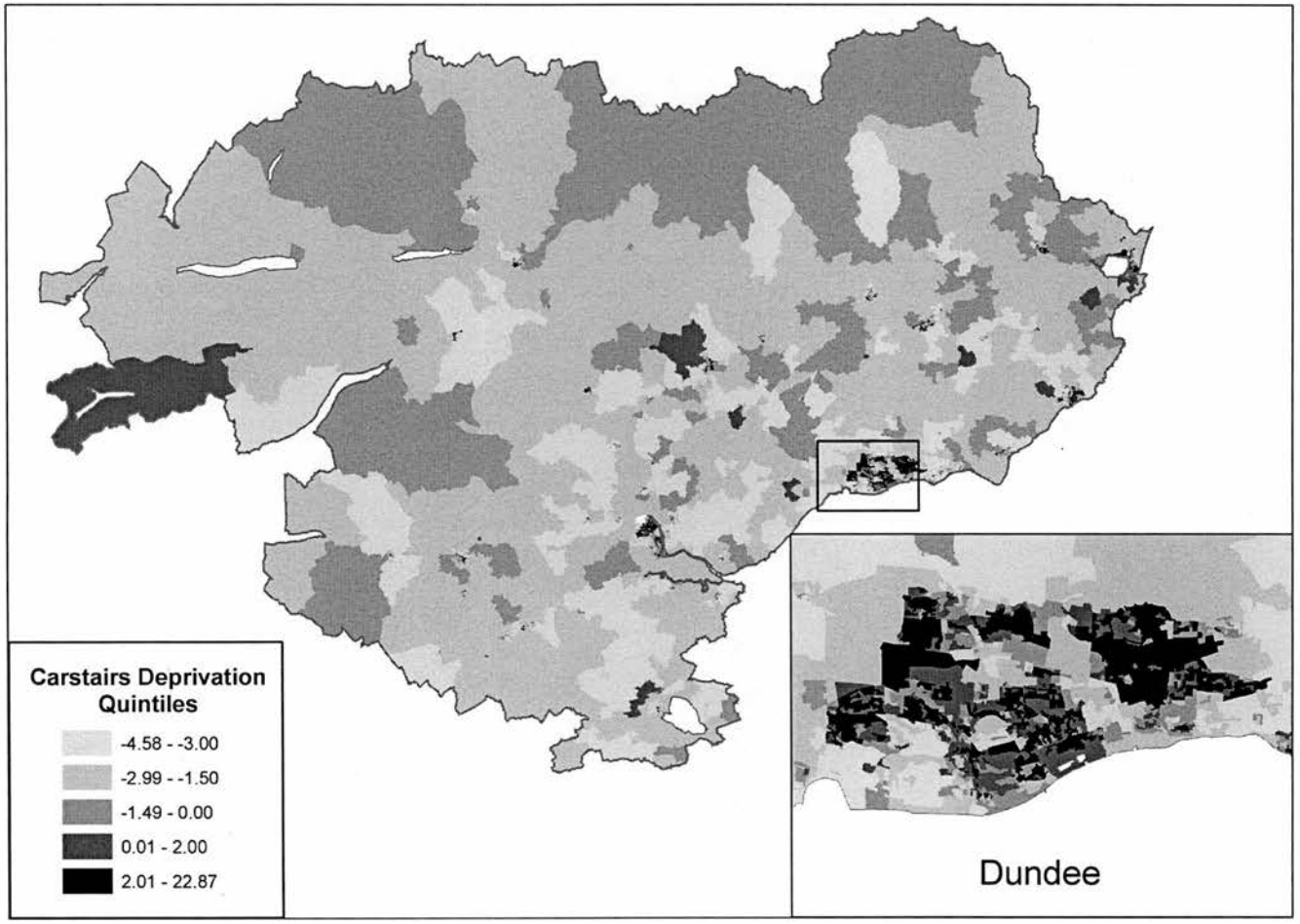


Figure 4.5 Carstairs Deprivation Index 2001 for Tayside output areas (created using boundaries from UK Borders and deprivation data from 2001 Census).

4.3 The Diabetes Audit and Research Tayside Scotland (DARTS) dataset

The diabetes data used in this thesis are drawn from the Diabetes Audit and Research Tayside Scotland (DARTS) dataset (see Morris, Boyle, MacAlpine et al., 1997 for more details). This dataset is the result of an ongoing project to combine clinical diabetes related datasets in order to provide a comprehensive register of people with diabetes in Tayside along with associated clinical data. This is possible because each patient in Scotland is allocated a unique ten-digit identifying number called the Community Health Number (CHI). This number is recorded, along with their name, address, postcode, general practitioner, death and date of death of the patient, in a continuously updated computer system called the Community Health Master Patient Index (Morris, Boyle, MacAlpine et al., 1997). The starting point for DARTS is to select from the Scottish data, all patients in Tayside as identified by the Community Health Master Patient Index. The Community Health Number is used as the patient identifier in all healthcare activities in Tayside, including both primary and secondary care. Therefore, data from diabetes-related datasets can be electronically linked to the records of the Tayside population using the CHI.

To maximise the complete ascertainment of cases of diabetes in Tayside, DARTS incorporates data from the following sources:

1. *Diabetes prescription database* – identifies any Tayside resident dispensed antidiabetic drugs or diabetic monitoring devices.

2. *Hospital diabetes clinics* – identifies Tayside residents attending a diabetic clinic according to the four hospital datasets used in Tayside (Morris, Boyle, MacAlpine et al., 1997).

3. *Mobile diabetes eye units* – identifies Tayside residents attending community screening for diabetic retinopathy and includes routine data on Type and duration of diabetes. Every general practice in Tayside is invited to refer all patients with diabetes for screening.

4. *Regional biochemistry database* – analyzes results of diagnostic blood tests for diabetes for Tayside residents. A positive diagnosis of diabetes in DARTS was conferred from the results of appropriate tests.

5. *The Scottish Morbidity Record (SMR1)* – identifies Tayside patients discharged from hospital with a primary or secondary diagnosis of diabetes.

Although there will still be a number of undiagnosed diabetes sufferers in Tayside, this is the most comprehensive register of Type 1 and Type 2 diabetes in the UK.

The classification of diabetes Type (i.e. Type 1 or Type 2) of the persons captured by DARTS was undertaken using the following algorithm: if the person was treated with insulin and 35 years or less at the time of diagnosis, or if they were treated with insulin within a month of diagnosis, they were recorded as having Type 1 diabetes. If they

were treated by oral hypoglycaemic agents and over 35 years old at diagnosis, regardless of treatment, they were recorded as having Type 2 diabetes. The resulting dataset (DARTS) is continually validated by a team of three research nurses who visit GP practices and review medical records to make sure the diagnosis and categorisation of diabetes recorded on DARTS is correct (see Morris, Boyle, MacAlpine et al., 1997 for further details).

Data was obtained from DARTS including date of birth, sex, Type of diabetes, date of diagnosis, and date of death. The geographical distribution of the diabetes data was derived from patient postcodes which were used to allocate the cases to output areas (the smallest areas for which Census data is available) before data retrieval. Using the output area of each case the diabetes data could then be related to the Census data, including socio-economic variables and proxy measures of population mixing.

The cohort of people with diabetes that were analysed here varies depending on the specific research question. Thus, the Type of diabetes, the age groups involved, and the time periods of the study all vary between the different analyses. Also, the dynamic nature of the DARTS database means that the earlier analyses drew upon data collated for 1998 onwards. The more recent analyses took advantage of further validation of more historic data. Thus, Manuscripts 1, 2 and 3 use data collected from 1998 onwards, while Manuscript 4 (a later study considering the migration of people with diabetes in Tayside) followed a cohort of people diagnosed with diabetes between 1985 and 1994.

Ethical approval was required both for the project as a whole and to allow the necessary DARTS data to be downloaded and analysed within the School of Geography & Geosciences at the University of St Andrews. An application for ethical approval was submitted to the Tayside Committee on Medical Research Ethics and duly awarded on the 30th July, 2002. Similarly, written ethical approval was also sought and granted at a later date for the study concerning the uptake of glucose monitoring strips, as an extension to a previous project conducted by Dr Josie Evans from the University of Dundee. Concordant with the NHS guidelines on patient confidentiality, the individual patient data taken from DARTS was anonymised and aggregated for small areas (output areas) for use in this thesis.

4.4 The incidence of diabetes in Tayside

The data extracted from DARTS shows that between 1998 and 2001, there were 220 diagnosed cases of Type 1 diabetes, of which 73 were children aged 0-14 years, and 3,920 diagnosed cases of Type 2 diabetes. This equates to a crude incidence rate for Type 1 diabetes of 14.1 per 100,000 people per year and a childhood incidence rate of 53.4 per 100,000 children per year. The incidence of childhood diabetes recorded on the DARTS system between 1998-2001 is considerably greater than the rate of 23.5 per 100,000 children reported for Tayside between 1984-2000 (see section 3.2.2) by the Scottish Study Group for the Care of Diabetes in the Young (published in Scottish Diabetes Survey Monitoring Group, 2004). This disparity likely reflects the sharply increasing incidence of Type 1 childhood diabetes since 1984.

Meanwhile the crude incidence rate of Type 2 diabetes in Tayside is 25.2 per 10,000 people (note Type 2 diabetes rates are provided per 10,000 people, rather than per 100,000 people as for Type 1 rates). Given that most studies of Type 2 diabetes are based on prevalence it is difficult to place this incidence rate into context. However, given the increasing incidence of Type 2 diabetes (Gatling, Budd, Walters, Mullee, Goddard, & Hill, 1998) the rate recorded by DARTS would seem comparable to rates recorded by Barker, Gardner, & Power in 1982 of incidence in 9 British towns which ranged from 7 to 23 per 10,000 (see page 87).

The DARTS data also shows that the incidence of both Type 1 and Type 2 diabetes varies widely across small areas within Tayside. Standardised incidence rates were calculated by aggregating diabetes data from output areas into the Census Area Statistics (CAS) sectors, into which they neatly fit. The denominator populations for the CAS sectors were taken from the 2001 Census and the rates were standardised to the overall Scottish population age structure. The standardised rates allow areas with different population structures to be compared directly. Figure 4.6 & Figure 4.7 show age and sex adjusted incidence rates by CAS sectors. The incidence rates of Type 1 diabetes ranged from 0.0-66.9 per 100,000 population and the overall Tayside rate was 14.7 per 100,000 (Figure 4.6). However, due to the relatively small number of incident cases of Type 1 diabetes in Tayside during the study period (1998-2001), 22 of the 85 CAS sectors had no recorded cases at all. While the rates varied a good deal, the 95% confidence intervals in Figure 4.6 are indicative of the relatively small number of Type 1 diabetes.

There is, however, statistically significant geographic heterogeneity in the standardised incidence rates for Type 2 diabetes (Figure 4.7). The rates ranged between 0.0-46.1 per 10,000 with an overall standardised rate of 23.5 per 10,000 for the whole of Tayside (Figure 4.7). Due to the larger number of cases, the confidence intervals are much narrower than for Type 1 diabetes.

When Type 1 incidence rates are mapped it is difficult to distinguish any geographic patterns (Figure 4.8). The small numbers of cases mean the rates are prone to random fluctuation particularly in the less populated rural areas of Tayside. However, it is discernable that Type 1 incidence rates are not particularly high in the deprived areas of Dundee. No linear correlation was found with the Carstairs score of the CAS sector, or indeed population density, which has been shown to be related to Type 1 incidence in a previous study in Tayside (Waugh, 1986). However, given the small numbers of cases involved and the number of CAS sectors recorded as having no cases, it does not make a great deal of sense to look for linear relationships with other variables. Poisson regression models are therefore adopted in the analyses presented in the following chapters which consider Type 1 diabetes.

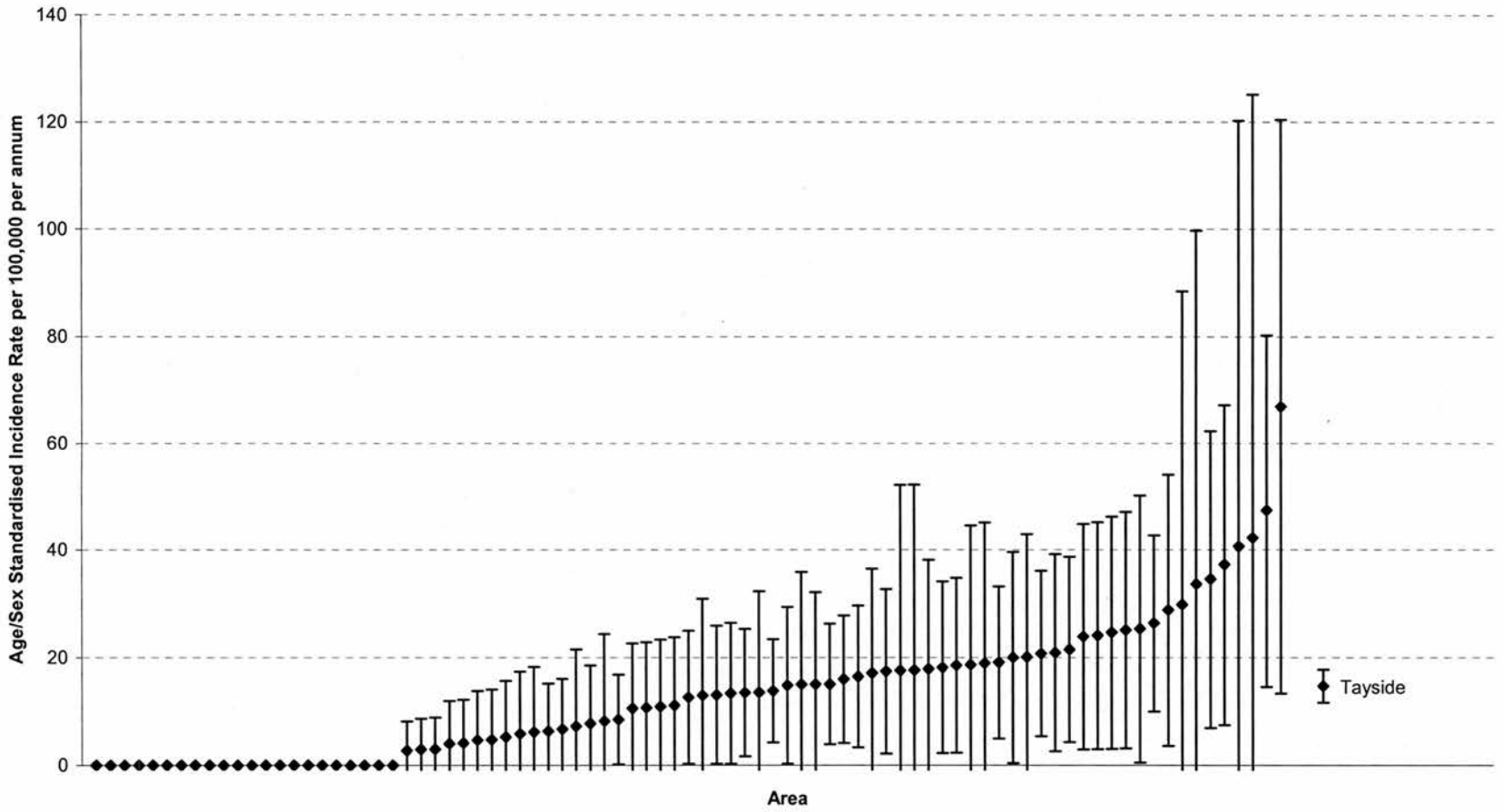


Figure 4.6 Age/Sex standardised Type 1 diabetes incidence by CAS sector in Tayside for 1998-2001. The rate for the Tayside Health Board is shown on the right-hand end of the figure. (Data obtained from DARTS).

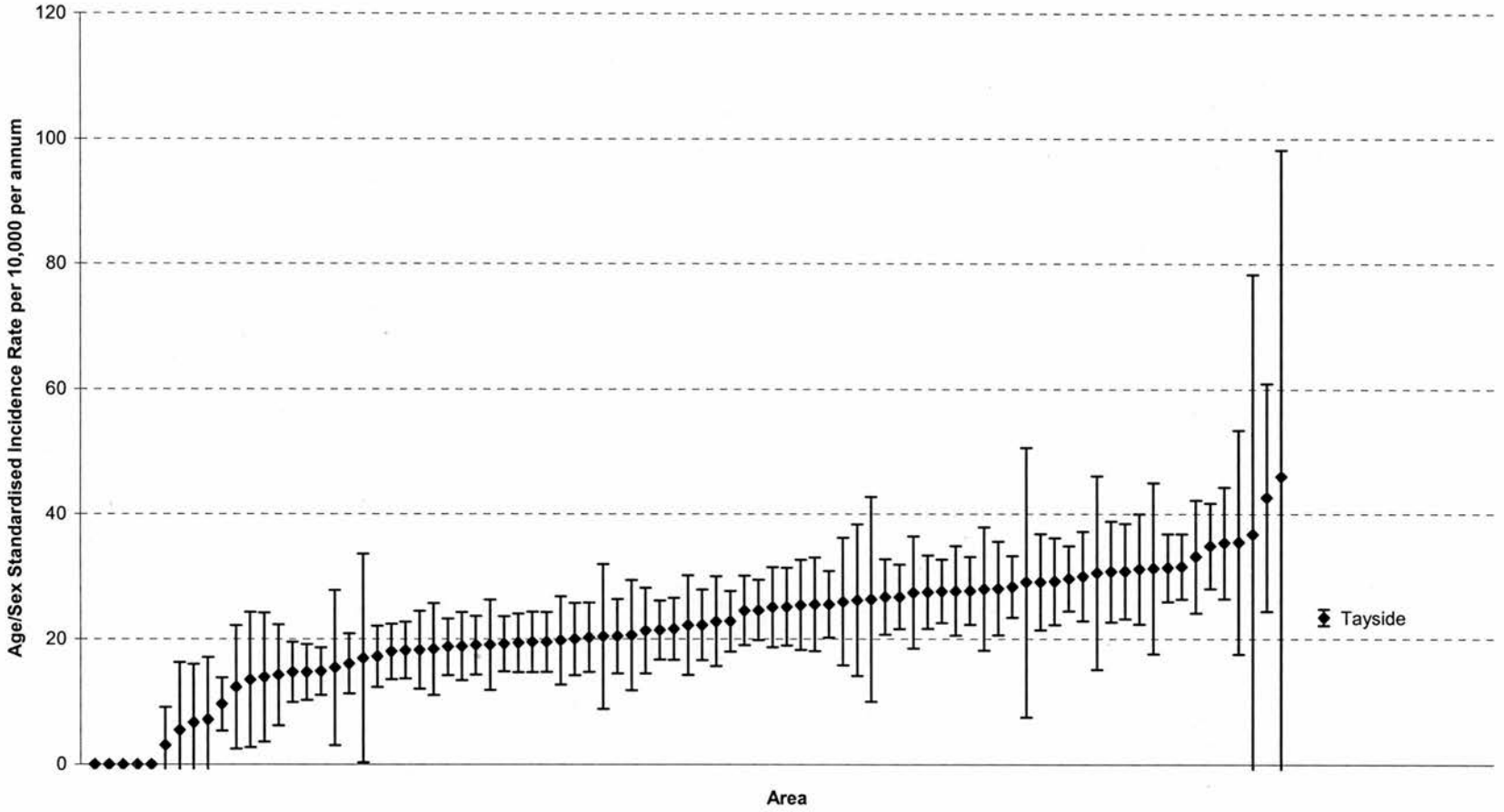


Figure 4.7 Age/Sex standardised Type 2 diabetes incidence by CAS sector in Tayside for 1998-2001. The rate for the Tayside Health Board is shown on the right-hand end of the figure. (Data obtained from DARTS)

Meanwhile, and as one would expect, Type 2 diabetes incidence appears to be high in the more deprived areas of Dundee (Figure 4.9). Although Type 2 incidence rates also fluctuate more in the rural areas of Tayside, on average the rates appear to be generally lower in these areas. When the Carstairs Index is correlated with the Type 2 standardised incidence rates, a significant and strong positive correlation co-efficient of 0.425 ($p<0.000$) is observed. The relationship between Type 2 diabetes incidence and deprivation is illustrated in a scatter graph in Figure 4.10, which also indicates an R-square value of 0.181 suggesting that 18% of the variation in Type 2 incidence between CAS sectors could be explained by differences in the level of deprivation. Population density was also correlated with Type 2 incidence, although the relationship was marginally insignificant, and probably reflects the co-variation of population density and deprivation.

4.5 Conclusions

Type 1 and Type 2 diabetes incidence have very different geographies within small areas of Tayside. Small numbers of incidence cases of Type 1 diabetes make rate estimations difficult to interpret, however the rates were relatively low in deprived urban areas, suggesting there may be a rural bias similar to that witnessed elsewhere in Scotland (Patterson & Waugh, 1992). Conversely, Type 2 diabetes incidence has shown considerable geographic variability and rates were particularly high in the deprived urban areas of Tayside, such as those in Dundee. Given these observations,

later sections of this thesis will focus on: a) population mixing mechanisms which may explain the rural bias found in Type 1 diabetes incidence, and b) the relationships between Type 2 diabetes incidence and deprivation.

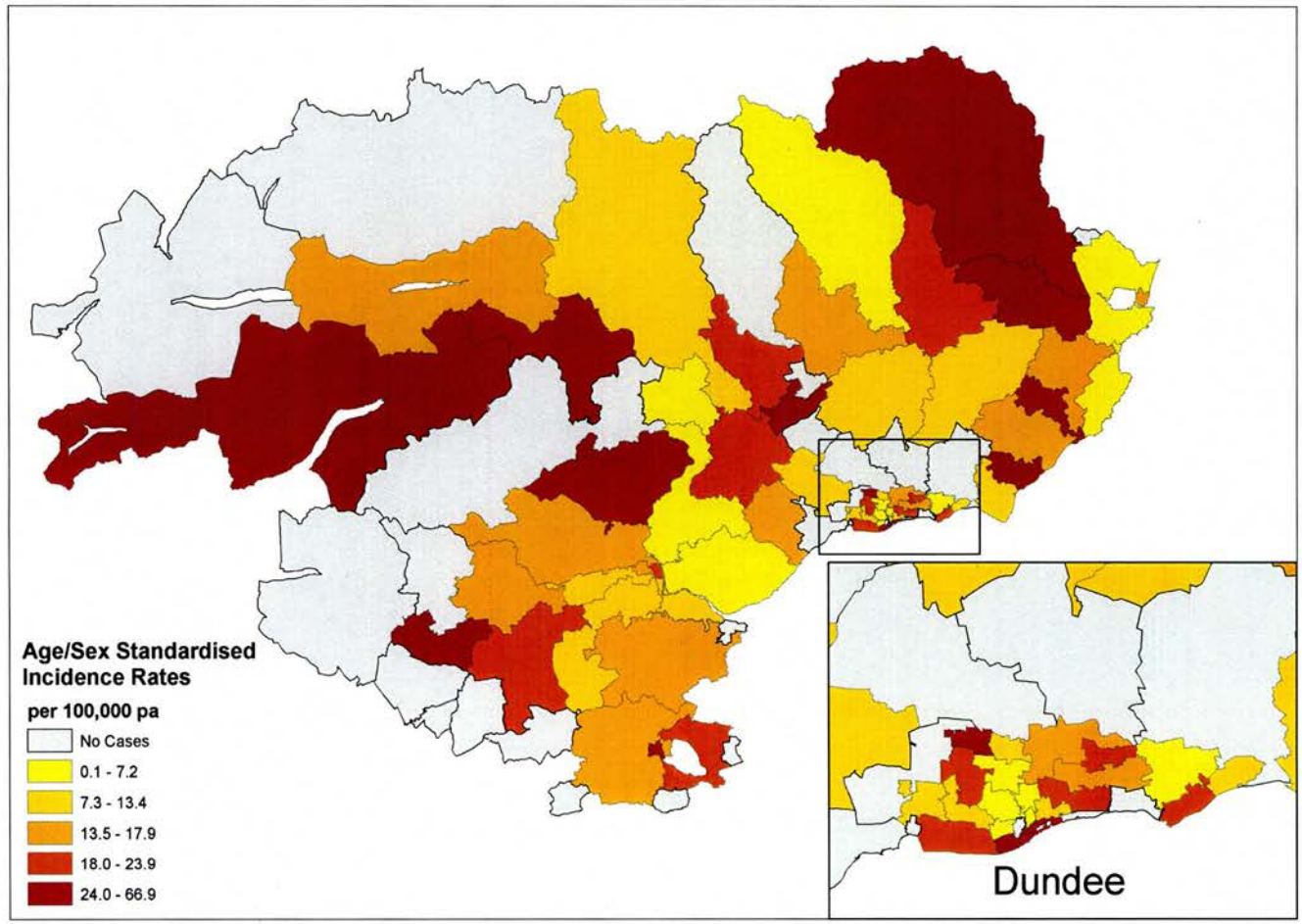


Figure 4.8 Map of age/sex standardised rates for Type 1 diabetes incidence in Tayside by CAS sector, 1998-2001. (Created using boundaries from UK Borders and DARTS data).

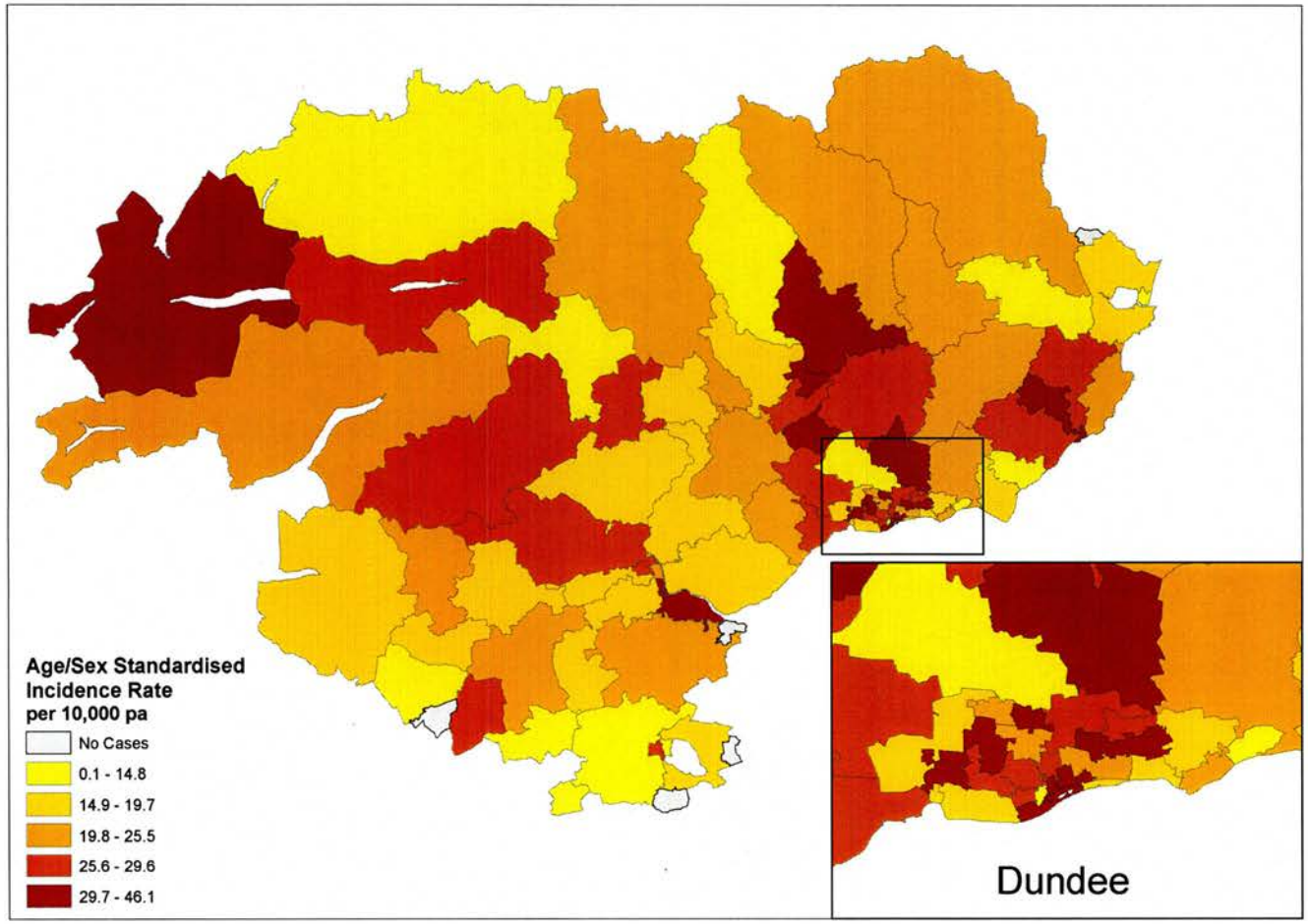


Figure 4.9 Map of age/sex standardised rates for Type 2 diabetes incidence in Tayside by CAS sector, 1998-2001. (Created using boundaries from UK Borders and DARTS data).

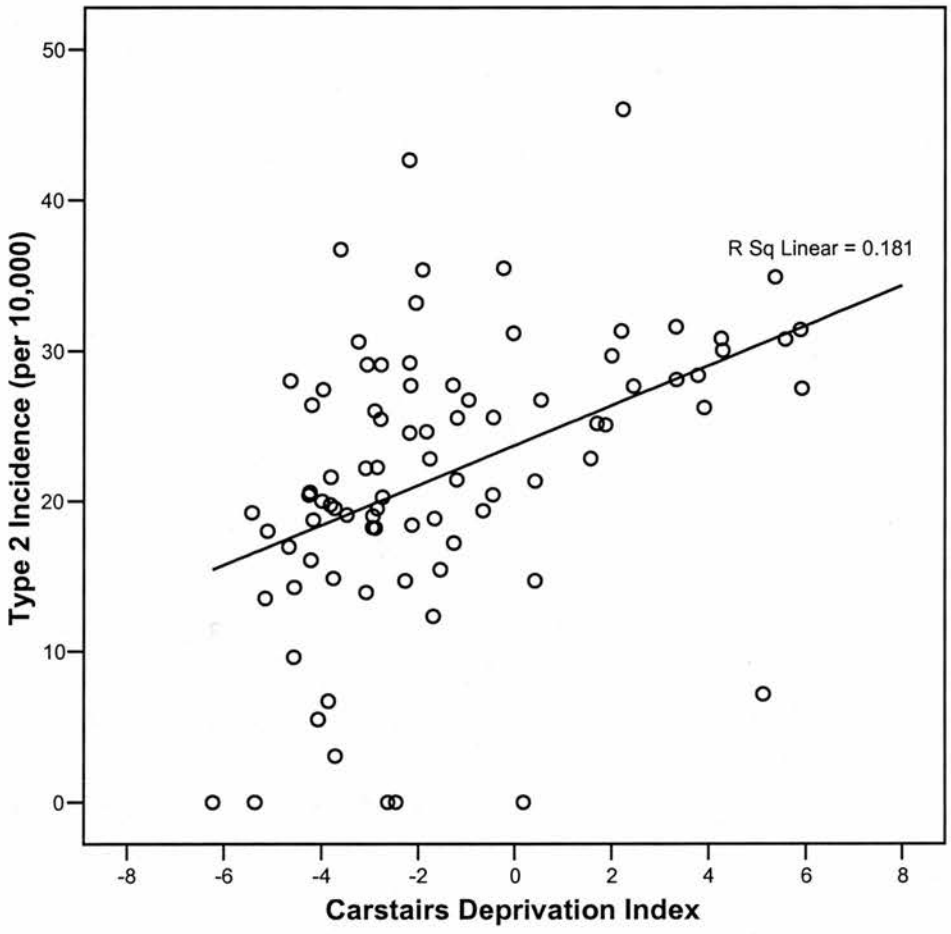


Figure 4.10 Type 2 diabetes age/sex standardised incidence against Carstairs Deprivation Index for CAS sectors in Tayside, 1998-2001. (Created using DARTS data and deprivation data from the 2001 Census).

CHAPTER 5 – INTRODUCTION TO MANUSCRIPTS

The results of this thesis are presented in the form of four manuscripts, all of which have been accepted for publication or are currently in review. This chapter summarises the research aims behind this study and how each manuscript contributes to the overall objective of the research project: to improve the understanding of geographic variations in the incidence of diabetes mellitus in Tayside, Scotland.

The review of the aetiology of diabetes, its potential environmental causes, and its geography, provided in Chapters 2, 3, & 4, highlight many gaps in our knowledge regarding the nature and the causes of geographic variation in the incidence of diabetes. Indeed, in the case of Type 2 diabetes very little is known about its geography either in the UK or worldwide (section 3.3). Consequently, there is a clear need to further explore and understand geographic variations in diabetes incidence along with the social determinants and processes which create them. Such insights will provide a greater understanding of the aetiology of diabetes in Tayside, which will have relevance in the rest of the UK and in other developed countries, and may also help to shape health policies designed to counteract the growing diabetes epidemic.

The availability and utilisation of high quality diabetes data from DARTS, in association with geographic data analysis techniques and the use of Geographic Information Systems (GIS), can help us address these 'knowledge gaps'. In so doing, this thesis addresses a series of related topics via a number of research questions:

Type 2 diabetes incidence, deprivation and selective-migration

1. *Is Type 2 diabetes incidence related to socio-economic deprivation in small areas within Tayside?* - To date, there has been no study in the UK which has examined the relationship between Type 2 diabetes incidence and deprivation. This is an important issue, as identifying areas where Type 2 diabetes is more common (and where there may be more undiagnosed cases) should be a helpful policy tool.

2. *Is the relationship between socio-economic deprivation and Type 2 diabetes prevalence exaggerated by the effects of selective migration?* - Many studies of socio-economic status and Type 2 diabetes rely heavily upon cross sectional prevalence data (Benach, Yasui, Borrell et al., 2001; Connolly, Unwin, Sherriff et al., 2000; Evans, Newton, Ruta et al., 2000). However, this is problematic as the people with diabetes captured in these cross-sectional studies may have moved since developing the condition. Such mobility may alter the apparent relationship between Type 2 diabetes and socio-economic deprivation. If health-selective mobility is occurring, it is possible that the relationship between Type 2 diabetes and deprivation may be exaggerated. It is therefore important to know if people with Type 2 diabetes tend to reside in more deprived areas over time as a result of selective (im)mobility as this will affect the confidence we can have in the findings of cross-sectional prevalence studies.

The above research questions are addressed in Manuscript 1 (Chapter 6) – "Does health-selective migration following diagnosis strengthen the relationship between Type 2 diabetes and deprivation?"

Socio-spatial context and Type 2 diabetes incidence

3. *Is the incidence of Type 2 diabetes related to the wider socio-spatial context of where one lives?* - There is evidence that variations in deprivation in an area and its surrounds may be related to increased illness (Boyle, Gatrell, & Duke-Williams, 1999; Boyle, Gatrell, & Duke-Williams, 2004). This potentially important finding relates directly to the context in which people live. Although, the results from the first analysis above suggest that deprived small areas are more likely to have increased incidence of diabetes, it is not known whether this increased risk is also associated with the deprivation context in the surrounding area. This manuscript examines whether Type 2 diabetes incidence is influenced by the deprivation circumstances of both the local area and its surrounds.

4. *Theoretical mechanisms which may link area context and diabetes incidence* – Following on from the previous question, two alternative hypotheses can be suggested which might explain the influence of surrounding areas on health: one applies the 'relative inequality hypothesis' to small areas and the other the 'pull-up/push-down' hypothesis. The former hypothesis suggests that those living in more deprived areas may suffer poorer health if the surrounding areas are

relatively less deprived, as a result of negative social comparisons. The opposite, pull-up/pull-down hypothesis suggests that the better social and physical conditions of surrounding areas may have a positive, material, effect on health. This analysis explores the evidence to support these hypotheses.

The above research questions are addressed in Manuscript 2 (Chapter 7) – entitled "Locality deprivation and Type 2 diabetes incidence in Tayside, Scotland: A local test of relative inequalities."

Childhood Type 1 diabetes, population mixing and the hygiene hypothesis

5. *In line with the hygiene hypothesis: is Type 1 diabetes more common in areas with low levels of population mixing, and hence less infection load?* – The hygiene hypothesis has been suggested as a possible mechanism in the aetiology of childhood Type 1 diabetes. In contrast to Type 2 diabetes, Type 1 diabetes appears to be less common in rural areas of Tayside. One possible explanation is that Type 1 diabetes, may be influenced by early contact with infections. In particular, children who come into contact with infections may develop immunity which protects againsts Type 1 diabetes. This manuscript therefore propose a new measure of population mixing to test whether areas with lower rates of mixing (and hence lower infection rates) have higher rates of Type 1 diabetes.

The above research question is addressed in Manuscript 3 (Chapter 8) – entitled "Childhood Type 1 diabetes, population mixing and the hygiene hypothesis."

Geographic access to pharmacies and glucose self-monitoring

6. *Is the uptake of glucose testing reagent strips (for self-monitoring) influenced by the distance between where people with Type 2 diabetes live and their nearest pharmacy?* – Glucose testing strips are used by patients with diabetes to monitor their blood sugar level. A previous study in Tayside showed that deprivation and age were related to the uptake of glucose testing strips (Evans, Newton, Ruta et al., 1999). This is a very important topic as self-monitoring plays an important role in diabetes management, helping patients take control of their condition. It may also help to reduce the number of diabetes-related complications. However no study has considered geographical access to healthcare services as a determining factor of self-monitoring. This thesis explores whether geographic distance to dispensing pharmacies is related to strip uptake. Given concerns about the closure of rural, remote pharmacies, this analysis has direct policy implications.

The above research question is addressed in Manuscript 4 (Chapter 9) – entitled "Geographic access to pharmacies and the uptake of reagent strips for glucose self monitoring by people with Type 2 diabetes in Tayside, Scotland."

The basic methodology for three of the four manuscripts was to test the relationship between the incidence of certain Types of diabetes (i.e. childhood Type 1 diabetes; or Type 2 diabetes) and some measured geographic phenomena measured for the thesis (i.e. socio-economic deprivation; the levels of deprivation in the surrounding small areas; population mixing). Therefore there was a common aim behind these three manuscripts: to explore the geographic variation in the incidence of a particular Type of diabetes and to look at whether these variations can be explained by certain social process. Manuscript 1 extends this idea to look at how the socio-economic distribution of Type 2 diabetes changes over time, following diagnosis. Manuscript 4 takes a different form to the previous manuscripts and is concerned with the uptake of glucose testing strips rather than diabetes incidence. However, Manuscript 4 is still bound closely to the thesis, as it is concerned with geographic variation relating to diabetes in Tayside. The analyses in Manuscripts 2-4 used standard regression techniques often used in health geography.

Each of these papers provides a novel contribution to the growing, but still relatively small, literature on social and geographical influences on diabetes.

CHAPTER 6 – [MANUSCRIPT 1] DOES HEALTH-SELECTIVE MIGRATION FOLLOWING DIAGNOSIS STRENGTHEN THE RELATIONSHIP BETWEEN TYPE 2 DIABETES AND DEPRIVATION?

Matthew Cox[1], Paul J Boyle[1,2], Peter Davey[3], Andrew D Morris[4]

1. School of Geography & Geosciences, University of St Andrews, St Andrews, KY16 9AL
2. Social Dimensions of Health Institute, Universities of Dundee and St Andrews, DD1 4HJ
3. Health Informatics Centre, Division of Community Health Services, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY
4. DARTS/MEMO Collaboration, Divisions of Medicine and Therapeutics and Community Health Sciences, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY

Forthcoming in *Social Science & Medicine.*

6.1 Abstract

Geographical health inequalities have been demonstrated for Type 2 diabetes in many developed countries, with poorer areas tending to have higher rates than wealthier areas. Previous studies have considered diabetes prevalence, relying on cross-sectional data collected from registers or hospital admissions records. However, the environment that had most influence on the development of a person's diabetes may not have been the same environment in which they are identified in a prevalence study. We therefore investigate whether health selective migration confounds the relationship between diabetes and deprivation by following a cohort of people with Type 2 diabetes from diagnosis until the end of the study, 8 to 18 years later. Our results demonstrate, first, that there is a significant relationship between material deprivation and diabetes incidence. Second, people with Type 2 diabetes in Tayside have become more concentrated in relatively more deprived areas over time, strengthening the relationship between diabetes and material deprivation. Third, and perhaps unexpectedly, this strengthening effect results primarily from selective immobility, rather than selective migration. We conclude that care should be taken when evaluating the relationship between diabetes and deprivation in cross sectional studies.

Keywords Tayside, Scotland; Type 2 diabetes; deprivation; selective migration.

6.2 Introduction

Type 2 diabetes occurs when the sensitivity of the body's cells to insulin, and/or the ability to produce insulin, becomes impaired. Insulin is the key hormone involved with the storage and controlled release of chemical energy available from food, and therefore this impairment results in chronic hyperglycaemia (increased blood glucose). In the long-term the altered metabolic state of hyperglycaemia results in micro- and macro-vascular damage and, therefore, eye, kidney, nerve and artery damage are all common complications of the disease. Although the underlying aetiology of Type 2 diabetes is unclear, there are a number of well documented risk factors. Type 2 diabetes is strongly associated with age, with the average age of diagnosis in the UK around 52 years old (UK Prospective Diabetes Study Group, 1988), although more recent evidence suggests this is increasing as the population is ageing and becoming more prone to diabetes. Behavioural risk factors are also important, particularly diet and lack of exercise (UK Prospective Diabetes Study Group, 1988). Hypertension and diabetes also frequently coexist, and people with hypertension are thought to be 2.5 times more likely to develop Type 2 diabetes (Gress, Nieto, Shahar, Wofford, & Brancati, 2000).

The prevalence of Type 2 diabetes is rising throughout the developed world (Amos, McCarty, & Zimmet, 1997; Passa, 2002; Wild, Roglic, Green et al., 2004), including the UK (Gatling, Budd, Walters et al., 1998; Harvey, Craney, & Kelly, 2002), and several cross-sectional (prevalence) studies have demonstrated that it is positively

related to material deprivation (Connolly, Unwin, Sherriff et al., 2000; Evans, Newton, Ruta et al., 2000; Meadows, 1995; Whitford, Griffin, & Prevost, 2003). However, to date, there have been no incident studies that have considered the relationship between Type 2 diabetes and deprivation, due mainly to the lack of reliable register information. This study investigates the relationship between Type 2 diabetes and deprivation at both the time of diagnosis ('incidence'), and at a specified later point ('prevalence').

This is relevant because recent longitudinal studies have shown that the relationship between deprivation and a variety of health outcomes may change over time because of health-selective (im)mobility (Boyle, Norman, & Rees, 2002; Brimblecombe, Dorling, & Shaw, 1999; Norman, Boyle, & Rees, 2005). Thus, a sorting process may occur where those in poor health are more likely to move into (or remain in) deprived residential areas and those in better health are more likely to move into (or remain in) less deprived areas.

Many of the previous studies which have examined the effects of health-selective migration have considered deprivation circumstances at the time of mortality or illness and compared these to deprivation circumstances in some previous period (e.g. Boyle, Norman, & Rees, 2002; Norman, Boyle, & Rees, 2005). This study is different because it follows the mobility trajectories of people from the time of diagnosis of a chronic condition (Type 2 diabetes). This is sensible, as it is plausible that some people with diabetes will be forced to migrate into lower cost housing because of the difficulties of maintaining their income in declining health, while healthy people may be more able to move into better housing areas. If so, cross-sectional prevalence studies, which

implicitly assume that material deprivation and factors associated with it influences diabetes, may be misleading as they ignore health-selective migration processes that occur after diagnosis.

Given this problem three alternative interpretations of the empirical relationship between diabetes and deprivation in prevalence studies could be: individual and area characteristics associated with deprivation have an important role in the aetiology of diabetes; the development of diabetes causes people to reside in more deprived areas as a result of health selective migration (reverse causation); deprivation is related to diabetes, but health selective processes further strengthen this relationship. This study therefore uses a unique Scottish data resource to examine three related hypotheses:

i) the incidence of Type 2 diabetes is positively associated with material deprivation;

ii) health selective (im)mobility strengthens the relationship between Type 2 diabetes and deprivation following diagnosis;

iii) the strengthening of the relationship between Type 2 diabetes and deprivation is caused mainly by the migration of diabetes sufferers into more deprived areas.

If such a sorting process is demonstrated we may need to be wary of the interpretation of prevalence studies that relate diabetes to ecological measures of socio-economic status, such as material deprivation.

6.3 Data and Methods

The Diabetes Audit and Research in Tayside, Scotland (DARTS) population-based database (Morris, Boyle, MacAlpine et al., 1997) is a comprehensive and reliable diabetes register, employing record linkage of multiple sources and validation by a team of dedicated nurses. From this, a cohort of people with Type 2 diabetes were identified as those 6199 subjects diagnosed between 1985 and 1994 in Tayside, Scotland. For each case we identified a residential postcode at the time of diagnosis and at the end of the study in November 2002, or at the time of death if before November 2002. The residential postcodes of the patients at diagnosis (incidence) and at the end of the study in 2002 (prevalence) or at their time of death were allocated to one of 669 'Consistent Areas Through Time' (CATTs) which fell within Tayside Health Board (Exeter, Boyle, Feng, Flowerdew, & Schierloh, 2005). These small geographical areas have populations of around 500 and allow data from the 1981, 1991 and 2001 censuses to be aggregated neatly into them. This is valuable, as the population denominators and deprivation scores are calculated for a consistent geographical basis throughout this analysis, removing the additional methodological and interpretational difficulties that result in studies of change over time because of boundary changes (commonly referred to as the 'modifiable areal unit problem'; Openshaw, 1984).

Of the cases, 469 had incomplete records, had moved out of the region, or had a postcode which fell within one of three CATTs that crossed the Tayside Health Board boundary and they were excluded from the study. The final analysis was based on a cohort of 5730 people with Type 2 diabetes for whom we had two residences recorded: one at diagnosis and one at the end of the study/time of death. At this point, the cohort was divided into three groups for whom results are reported separately in the remainder of this paper. The first included those that survived to the end of the study period (2002); the second included those in the cohort who died between 1996 (approximately the half way point of the study) and 2002; and the third included those who died before 1996. Table 6.1 shows the number of cases in each of our three groups and the mean age of diagnosis. The majority of peoples with diabetes in our sample survived the entire period and were, on average, diagnosed younger than those who died during the study period. Those who died before 1996 were older at diagnosis than those who died post-1996, indicating a relationship between late diagnosis and shortened life expectancy. The cases excluded from the study were in general diagnosed at a younger age than the study cohort (males 56.9 ± 14.8 s.d. years old; females 61.8 ± 15.6 s.d. years old).

We compared the distribution of these three groups of diabetes sufferers by deprivation of their area of residence. The Carstairs score (Carstairs & Morris, 1991) is a commonly used deprivation score designed specifically for use in Scotland. The score is calculated for each CATT by combining four socio-economic variables from the UK Census into a single index., The variables are: % of residents in households with no car as a proportion of all residents in households; % of persons in households with 1 or

more persons per room as a proportion of all residents in households; % of residents in households with an economically active head of household in social class IV or V (semi-skilled and unskilled occupational groups, respectively) as a proportion of all residents in households; and % of unemployed male residents aged over 16 as a proportion of all economically active male residents aged over 16. To allow the variables to be combined they are first standardised using 'Z-scores'. If the variable score for a CATT is the same as the mean for all areas then the standardised score will be zero. The standardised Z-scores for each variable are then added together to form the Carstairs Deprivation Index; CATTs with a negative Carstairs Index are less deprived than the rest of Scotland's CATTs and areas with a positive score are more deprived.

We calculated Carstairs scores for the Tayside CATTs for both 1991, to correspond with the diagnosis period, and for 2001 near the end of the study period (Figure 6.1 maps Carstairs deprivation in Tayside for 2001). The scores ranged between 10.62 (most deprived) and -5.15 (least deprived) in 1991 and 11.66 and -5.01 in 2001. These compare with a distribution of 16.41 to -5.27 in 1991 and 17.47 to -5.94 in 2001 for Scotland as a whole, demonstrating that Tayside had a fair mix of more and less deprived areas. Thus, we are able to compare the deprivation circumstances of our cases around both the time of diagnosis (1991 Carstairs score) and around the end of the study period in 2002 (2001 Carstairs score) or at the time of death post 1996 (2001 Carstairs score). For those who died prior to 1996, we use the 1991 Carstairs score for both the time of diagnosis and the time of death. For both 1991 and 2001, the CATTs were divided into population-weighted deprivation quintiles. Note that people with

Type 2 diabetes could change deprivation quintile either by moving to a different CATT, which fell in a different Carstairs quintile, or by staying within the same CATT, which itself changed Carstairs quintile over the period. Both scenarios are examined in this analysis and we are particularly keen to disentangle the changing deprivation circumstances of those who moved between CATTs and those who did not.

For all the groups, age (5 year age groups up to 85+) and sex standardised incidence ratios (SIRs) were calculated based on the population weighted deprivation quintile of the place of residence at diagnosis (between 1985 and 1994). SIRs were then calculated based on the deprivation quintile of the place of residence at the end of the study in 2002, or at the time of death for the groups who died before and after 1996. The denominator data were extracted from the relevant 1991 and 2001 Census. We also calculated 95% confidence intervals for all the SIRs. When comparing the SIRs, if the confidence intervals did not overlap the difference between the SIRs was considered to be statistically significant.

6.4 Results

Table 6.2 provides the raw numbers of people with diabetes whose area of residence became more or less deprived during the study. For the groups that survived the study or died between 1996 and 2002, 'non-movers' tended to become more concentrated in deprived CATTs over the period, with net transitions of 231 (530-299) and 105 (257-152) people into more deprived areas respectively. On the other hand, for all three

groups the movers tended to relocate to less deprived CATTs on average: a net balance of 118 (341-223) movers in the survivor groups moved to less deprived areas; 39 (177-138) more of the group that died between 1996 and the end of study moved to less deprived areas; and 41 (108-67) more of the group that died before 1996 moved to less deprived areas. Note, also, that for both survivors and those who died between 1996 and 2002, a considerably larger number of non-movers became more concentrated in deprived CATTs over time. On the other hand, a larger number of movers than non-movers became concentrated in less deprived CATTs over the period for both groups. This indicates that, in absolute terms, non-movers tended to concentrate in areas that become more deprived over the period (the areas they lived in tended to become more deprived around them) and movers tended to concentrate in less deprived areas (by moving between areas with different relative deprivation status).

Figures 6.2 - 6.9 go further to compare the specific deprivation circumstances of the three groups. Figure 6.2 shows those who survived to the end of the study period in 2002 using SIRs. For this group, who were relatively young at diagnosis compared to the other two groups, there was a slight tendency for them to become more concentrated in deprived areas over the period. The SIRs rose slightly for quintiles 3-5, but the differences between the time of diagnosis and the end of the study period were insignificant. However, separating the effects for those survivors who remained in the same CATT (Figure 6.3) and those that moved to a different CATT (Figure 6.4) between the date of diagnosis and the end of the study period, highlights an interesting difference. The deprivation gradient for those who remained in the same CATT was relatively flat, although the SIR for the most deprived quintile rose significantly during

the period (changes in deprivation circumstances for this group occurred because the characteristics of the CATT changed around them). On the other hand, the gradient for those who moved during the period was much steeper at the time of diagnosis, but became less steep over the period. Thus, those who moved tended to improve their circumstances and the slight rise in the overall survivor gradient displayed in Figure 6.2 was attributable to the worsening deprivation circumstances of those who did not move during the period.

Similar results are provided for those who died between 1996 and 2002. Figure 6.5 shows that overall the deprivation gradient steepened, with a slight reduction in the SIR for quintile 1 and quite a large, although insignificant, rise for quintile 5. Once again, the patterns for those who did not (Figure 6.6) and did (Figure 6.7) move between CATTs over the period were considerably different. The gradient for those who did not move steepened with a significant rise for those in quintile 5, while the gradient for those who moved reduced. Once again, those who moved improved their relative deprivation circumstances, while local conditions became worse for those who remained immobile.

Finally, the results were broadly similar for those who were diagnosed between 1985 and 1994, but died prior to 1996 (Figure 6.8). It should be recognised that some of these patients died quite soon after diagnosis (8% died within a month of diagnosis) and the average time between diagnosis and death was 3 years and 71 days. Also, it makes no sense to present the changing SIRs for the subset of this cohort who did not move, as the deprivation profile will not have changed since deprivation for this group was based

on the 1991 census at both the time of diagnosis and at the time of death (see above). Overall, the gradient decreased marginally for this group, but for the movers (Figure 6.9) the change was much more pronounced and the gradient narrowed in a manner similar to that observed for survivors and those who died after 1996.

To summarise the inequalities in Type 2 diabetes, the ratio between the SIRs for quintile 1 (most deprived) and quintile 5 (least deprived) are provided for all of the combinations above (Table 6.3). For each group we can compare the ratio at diagnosis to the ratio at the end of the study/time of death by mobility status: if the ratio has increased then inequalities can be said to have widened and if it has decreased then inequalities have narrowed. The ratios demonstrate that there is an overall widening of the diabetes gap between the most and least deprived areas for both the survivor group and for the group that died between 1996 and the end of the study. The widening inequalities observed in both these groups were attributable to those who remained immobile during the study period; the relative deprivation of the places they were in changed. In contrast, the ratios reduced for those people who moved during the study period suggesting a reduction of inequality. Non-movers were far less likely to change deprivation quintile than movers, but non-movers were around five times more numerous and therefore had a greater effect on the overall transition of people and SIRs.

6.5 Discussion

Evidence from previous ecological studies supports the premise that migration can change patterns of mortality and morbidity and may contribute significantly to the apparent widening of geographical health and mortality inequalities observed within the UK. Indeed O'Reilly (1994), writing in response to Phillimore, Beattie & Townsend 1994 regarding the 'Widening inequality of health in northern England 1981-91', notes that the increasing disparities in mortality observed may have been caused by selective migration. The mortality reduction seen in the 26 northern council areas was closely correlated with net population change, and the districts that experienced the largest net declines also experienced the smallest improvement in mortality. O'Reilly (1994) infers that people who are more likely to be in good health migrate away from such deprived areas, leaving behind a residualised group who may suffer worse health and have shorter life expectancies (O'Reilly, 1994; O'Reilly, Browne, Johnson, & Kelly, 2001). Other authors have also confirmed the negative relationship between population change and mortality (Davey Smith, Shaw, & Dorling, 1998, , 2001; Molarius & Janson, 2000), and population change and widening inequalities in mortality (Boyle, Exeter, & Flowerdew, 2004; Exeter, Boyle, Feng et al., 2005; Regidor, Calle, Dominguez, & Navarro, 2002).

Some earlier longitudinal studies of individuals have examined how people's circumstances change from a previous point in time and time of death, essentially

returning them to their previous circumstances. The choice of an appropriate starting point is debateable in these circumstances, as it is not clear when in a person's lifecourse deprivation and the various factors associated with it are most likely to have influenced their subsequent cause of death. Thus, Boyle, Norman, & Rees (2002) and Norman, Boyle, & Rees (2005) used a 20 year period, but it is uncertain in these retrospective studies whether the widening deprivation gradient resulted from people's illness causing them to move into more deprived areas prior to death, or whether moving into more deprived areas over the 20 year period hastened their demise.

This prospective analysis therefore examined how the deprivation circumstances change for a cohort of people with Type 2 diabetes *following diagnosis*. We examined three specific hypotheses. First, we have demonstrated that there is a significant positive relationship between Type 2 diabetes and deprivation at the time of diagnosis. The vast majority of previous studies have been cross-sectional prevalence studies, but this confirms the relationship at the time of diagnosis. For all three groups analysed here (survivors, those who died post-1996 and those who died prior to 1996) a clear gradient was present between diabetes incidence and material deprivation. However the gradient was strongest for the group of people who died before 1996, closely followed by the group who died from 1996 onwards, with a shallower gradient for the group who survived until the end of the study. This suggests that people with diabetes who are more likely to die relatively soon after diagnosis live in deprived quintiles, and much of this may be related to factors associated with late diagnosis, including late presentation.

Our second hypothesis stated that health-selective (im)mobility may strengthen the relationship between deprivation and Type 2 diabetes and this was indeed supported. However, the overall widening of the deprivation gap for our three groups was not significant. This may be related to the size of the sample, or the relatively short period between diagnosis and the end of the study (or death). Had the sample been larger, or the observation window been longer, it is possible that these results would have been significant.

Our third hypothesis was that the primary reason for the widening deprivation gap would be health-selective migration, with an assumption that those in poor health would be more likely to migrate towards deprived areas. In fact, this sorting hypothesis was not confirmed, as the primary reason for the widening gap was health-selective *immobility.* Those with diabetes who moved tended to improve their circumstances, while those who remained in the same CATT throughout experienced worsening deprivation. We need to be careful when comparing the mover and non-mover groups as the number of movers was smaller and, due to the sample size, more susceptible to random error. However, despite this problem our results concord with the argument that selective immobility may cause a residualisation of unhealthy individuals in poorer areas. It is immobile people with diabetes that tend to concentrate in more deprived areas and this will exaggerate the relationship between diabetes prevalence and material deprivation.

Some previous findings from studies that examine the relationship between limiting long-term illness (LLTI) and migration also support the findings of this study. Boyle,

Norman & Rees (2002) found that both short- and long-distanced migrants were less likely to suffer LLTI than non-migrants, lending weight to the reasoning that people in poorer health may be left behind in deprived areas by the more healthy. Additionally, Boyle and Duke Williams (2004) examined the flows of migrants with LLTI, reporting that migrants in poor health were more likely to move to less, rather than more, deprived places. This echoes our study, where the people with diabetes that migrate tend to move up the deprivation gradient. This movement may reflect a wish to take advantage of better health care facilities or support structures available in those areas, although it is not possible to test this using our data.

There is growing evidence that socio-economic status throughout the lifecourse may influence health outcomes in later life (Davey Smith, Hart, Blane, Gillis, & Hawthorne, 1997; Fourouhi, Hall, & McKeigue, 1997). People in more deprived areas are more likely to develop diabetes, and people with diabetes are more likely to remain in areas that become more deprived, further enhancing the relationship between diabetes prevalence and material deprivation. Ecological, cross-sectional studies that compare socio-economic circumstances with disease prevalence ignore such complexity. Overall, our results suggest that the relationship between Type 2 diabetes and deprivation is likely to be stronger in prevalence studies than in incidence studies, and that care should be taken when interpreting the results from the former. Even so, while the relationship with deprivation does appear to strengthen following diagnosis, this study also shows that Type 2 diabetes is over 50% more common in the most deprived areas compared to the least deprived areas at the time of diagnosis.

There are limitations to this study. Due to the Tayside focus of the DARTs dataset, we were unable to include people in the study who were diagnosed with Type 2 diabetes in Tayside but subsequently moved to an area outside the Health Board. Second, we have two time points; one at diagnosis and the other at data extraction/time of death. No information was available with regard to the movement of people with diabetes between these time points. However, this has little effect on the interpretation of our results as we were primarily interested in the general trends over time rather than following the deprivation experiences of individuals. This paper adds to the body of evidence which suggests that health-selective geographical mobility strengthens the relationship between morbidity and deprivation.

6.6 References

Amos, A.F., McCarty, D.J., & Zimmet, P. (1997). The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. *Diabetic Medicine*, 14(12), S7-S85.

Boyle, P., Norman, P., & Rees, P. (2002). Does migration exaggerate the relationship between deprivation and limiting long-term illness? A Scottish analysis. *Social Science & Medicine*, 55(1), 21-31.

Boyle, P., Exeter, D., & Flowerdew, R. (2004). The role of population change in widening the mortality gap in Scotland. *Area*, 36(2), 164-173.

Boyle, P.J., & Duke-Williams, O. (2004). Does migration exaggerate the relationship between material deprivation and health? In P.J. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The geograhy of health inequalities: views from Britain and North America* (pp. pp. 129-148). London: Ashgate.

Brimblecombe, N., Dorling, D., & Shaw, M. (1999). Mortality and migration in Britain, first results from the British Household Panel Survey. *Social Science & Medicine*, 49(7), 981-988.

Carstairs, V., & Morris, R. (1991). *Deprivation and Health in Scotland*: Aberdeen University Press

Connolly, V., Unwin, N., Sherriff, P., Bilous, R., & Kelly, W. (2000). Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of Type 2 diabetes mellitus in deprived areas. *Journal of Epidemiology and Community Health*, 54(3), 173-177.

Davey Smith, G., Hart, C., Blane, D., Gillis, C., & Hawthorne, V. (1997). Lifetime socioeconomic position and mortality: prospective observational study. *Bmj*, 314(7080), 547-552.

Davey Smith, G., Shaw, M., & Dorling, D. (1998). Shrinking areas and mortality. *Lancet*, 352(9138), 1439-1440.

Davey Smith, G., Shaw, M., & Dorling, D. (2001). Population change and mortality in men and women. *J Epidemiol Community Health*, 55(1), 9.

Evans, J.M.M., Newton, R.W., Ruta, D.A., MacDonald, T.M., & Morris, A.D. (2000). Socio-economic status, obesity and prevalence of Type 1 and Type 2 diabetes mellitus. *Diabetic Medicine*, 17(6), 478-480.

Exeter, D.J., Boyle, P., Feng, Z., Flowerdew, R., & Schierloh, N. (2005). The creation of 'consistent areas through time' (CATTs) in Scotland, 1981-2001. *Population trends*(119), 28-36.

Fourouhi, N., Hall, E., & McKeigue, P. (1997). A life course to diabetes. In D. Kuh, & Y. Ben-Shlomo (Eds.), *A life course approach to chronic disease epidemiology.* (pp. pp. 165-188).

Gatling, W., Budd, S., Walters, D., Mullee, M.A., Goddard, J.R., & Hill, R.D. (1998). Evidence of an increasing prevalence of diagnosed diabetes mellitus in the Poole area from 1983 to 1996. *Diabetic Medicine*, 15(12), 1015-1021.

Gress, T.W., Nieto, F.J., Shahar, E., Wofford, M.R., & Brancati, F.L. (2000). Hypertension and antihypertensive therapy as risk factors for Type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med*, 342(13), 905-912.

Harvey, J.N., Craney, L., & Kelly, D. (2002). Estimation of the prevalence of diagnosed diabetes from primary care and secondary care source data: comparison of record linkage with capture-recapture analysis. *J Epidemiol Community Health*, 56(1), 18-23.

Meadows, P. (1995). Variation of Diabetes-Mellitus Prevalence in General-Practice and Its Relation to Deprivation. *Diabetic Medicine*, 12(8), 696-700.

Molarius, A., & Janson, S. (2000). Population change and mortality in men and women. *J Epidemiol Community Health*, 54(10), 772.

Morris, A.D., Boyle, D.I.R., MacAlpine, R., EmslieSmith, A., Jung, R.T., Newton, R.W., & MacDonald, T.M. (1997). The diabetes audit and research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. *British Medical Journal*, 315(7107), 524-528.

Norman, P., Boyle, P., & Rees, P. (2005). Selective migration, health and deprivation: a longitudinal analysis. *Social Science & Medicine*, 60(12), 2755-2771.

O'Reilly, D. (1994). Health and social inequality in Europe. Migration from deprived areas may be a factor. *Bmj*, 309(6946), 57-58.

O'Reilly, D., Browne, S., Johnson, Z., & Kelly, A. (2001). Are cities becoming more unhealthy? An analysis of mortality rates in Belfast and Dublin between 1981 and 1991 to illustrate a methodological difficulty with ecological studies. *J Epidemiol Community Health*, 55(5), 354-355.

Openshaw, S. (1984). The Modifiable Areal Unit Problem., *Concepts and Techniques in Modern Geography Number 38.* Norwich: Geobooks.

Passa, P. (2002). Diabetes trends in Europe. *Diabetes-Metabolism Research and Reviews*, 18, S3-S8.

Phillimore, P., Beattie, A., & Townsend, P. (1994). Widening inequality of health in northern England, 1981-91. *Bmj*, 308(6937), 1125-1128.

Regidor, E., Calle, M.E., Dominguez, V., & Navarro, P. (2002). Inequalities in mortality in shrinking and growing areas. *J Epidemiol Community Health*, 56(12), 919-921.

UK Prospective Diabetes Study (1988). UK Prospective Diabetes Study. IV. Characteristics of newly presenting Type 2 diabetic patients: male preponderance and obesity at different ages. Multi-center Study. *Diabet Med*, 5(2), 154-159.

Whitford, D.L., Griffin, S.J., & Prevost, A.T. (2003). Influences on the variation in prevalence of Type 2 diabetes between general practices: practice, patient or socioeconomic factors? *British Journal of General Practice*, 53(486), 9-14.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes - Estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(5), 1047-1053.

6.7 Tables & figures

	Male		Female	
Group	Cases	Mean Age of Diagnosis	Cases	Mean Age of Diagnosis
Survived study period	1509	55.2 ± 11.0 s.d.	1294	58.1 ± 11.8 s.d.
Died 1996-2002	684	65.1 ± 10.5 s.d.	718	69.1 ± 10.4 s.d.
Died before 1996	764	69.5 ± 10.1 s.d.	761	74.0 ± 11.0 s.d.
Cohort	2957	61.2 ± 12.3 s.d.	2773	65.3 ± 13.0 s.d.

Table 6.1 Number and mean age (± standard deviation) of diagnosis of people with Type 2 diabetes in three groups within the cohort, by sex

Group	Overall	Non-movers	Movers
Survived study period			
Became less deprived	640	299	341
No change	1410	1155	255
Became more deprived	753	530	223
Died 1996-2002			
Became less deprived	329	152	177
No change	678	552	126
Became more deprived	395	257	138
Died before 1996			
Became less deprived	108	n.a.	108
No change	1350	1289	61
Became more deprived	67	n.a.	67

Table 6.2 Number of people with Type 2 diabetes moving between deprivation quintiles for three groups by mobility status

Group	Overall	Non-movers	Movers
Survived study period	1.48 to 1.53	1.05 to 1.40	3.18 to 1.89
Died 1996-2002	1.76 to 2.21	1.45 to 2.15	2.59 to 2.10
Died before 1996	1.86 to 1.81	n.a.	2.00 to 1.26

Table 6.3 The ratios between the SIRs for deprivation quintiles 1 and 5 at diagnosis and at the end of study/time of death for the three groups by mobility status

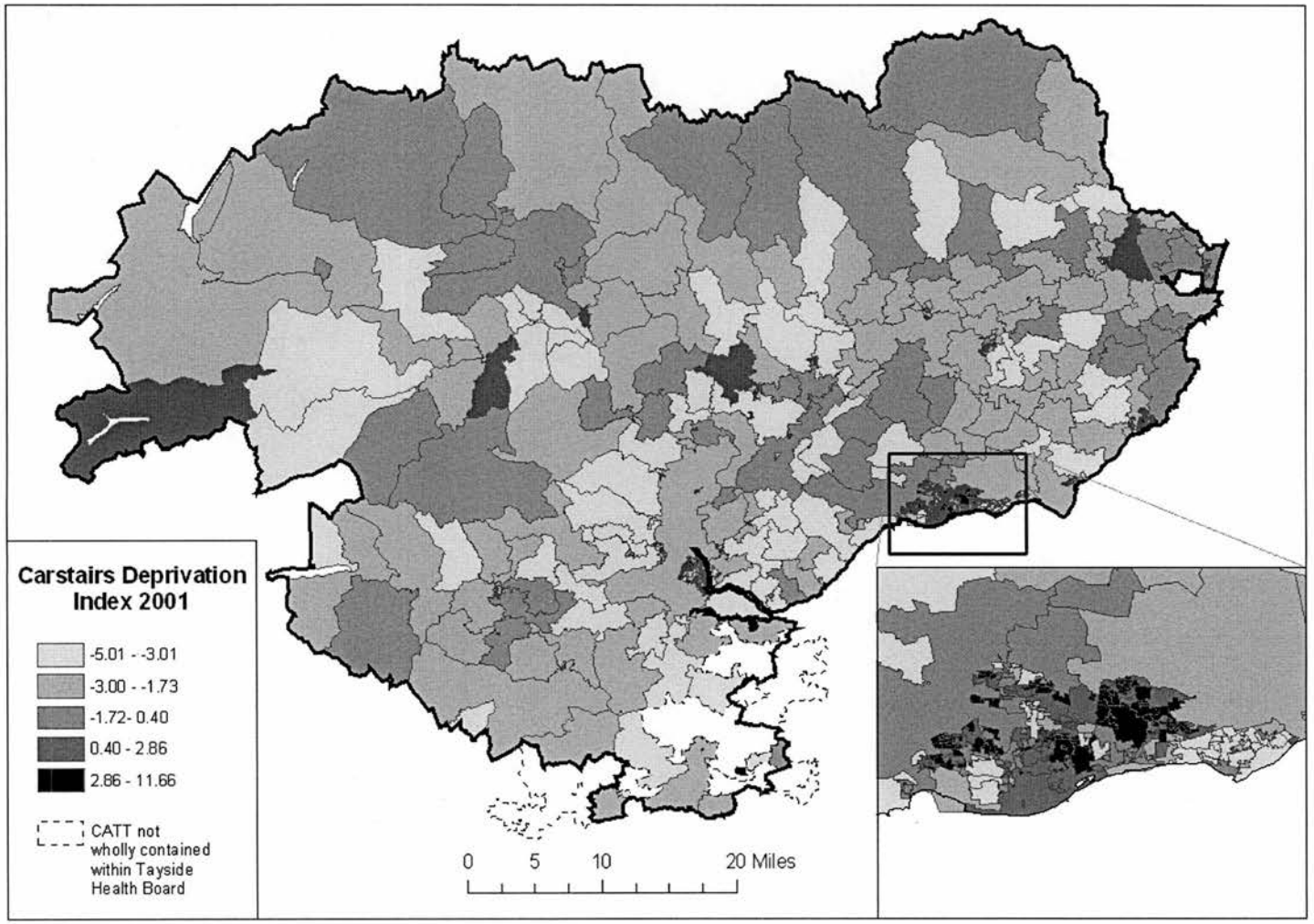


Figure 6.1 Carstairs deprivation by CATT in Tayside, Scotland, 2001

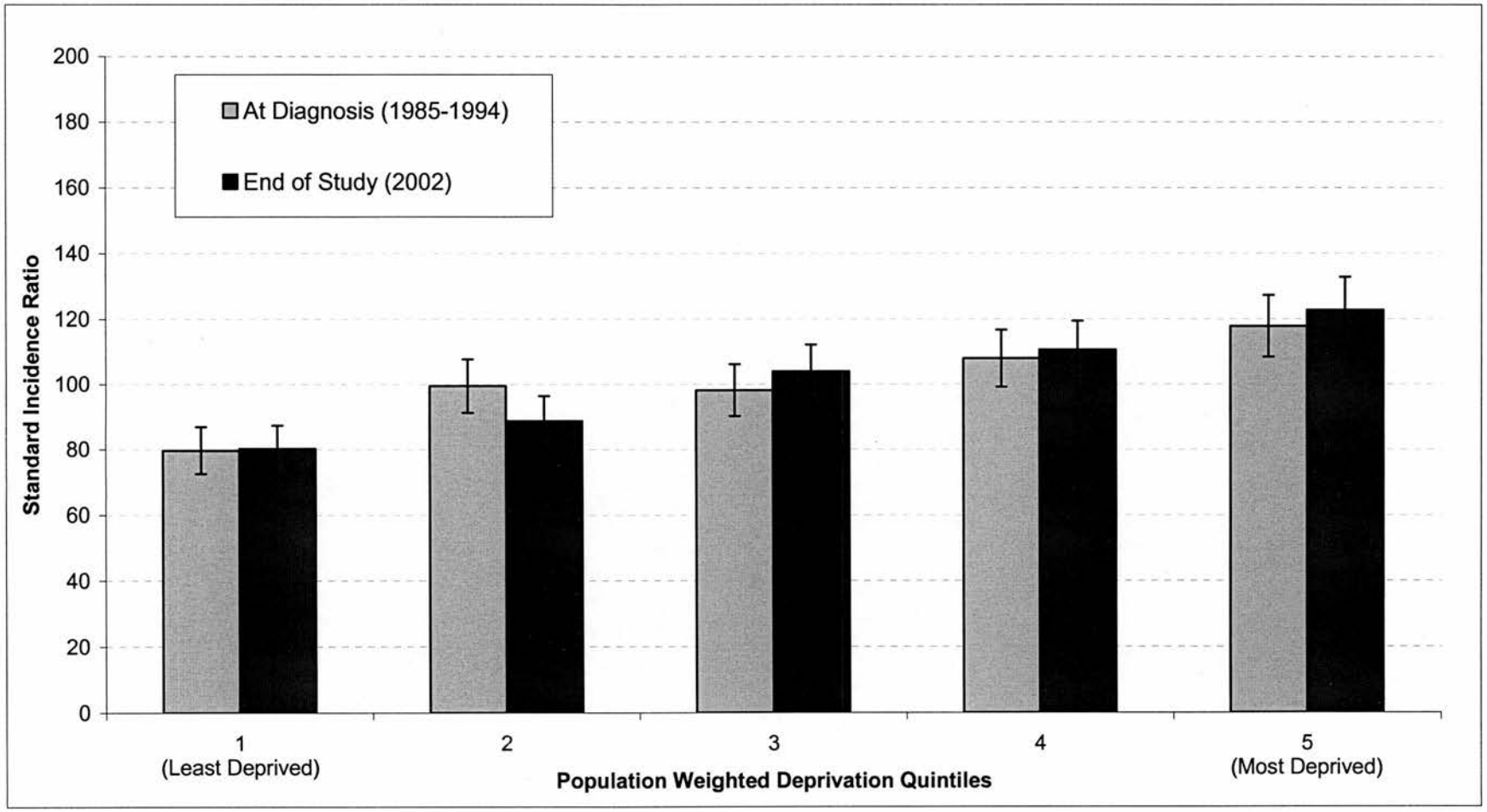


Figure 6.2 Standardised Incidence Ratios for Type 2 diabetes by deprivation at diagnosis and the end of the study period in Tayside, Scotland: survivors (bars are 95% confidence intervals).

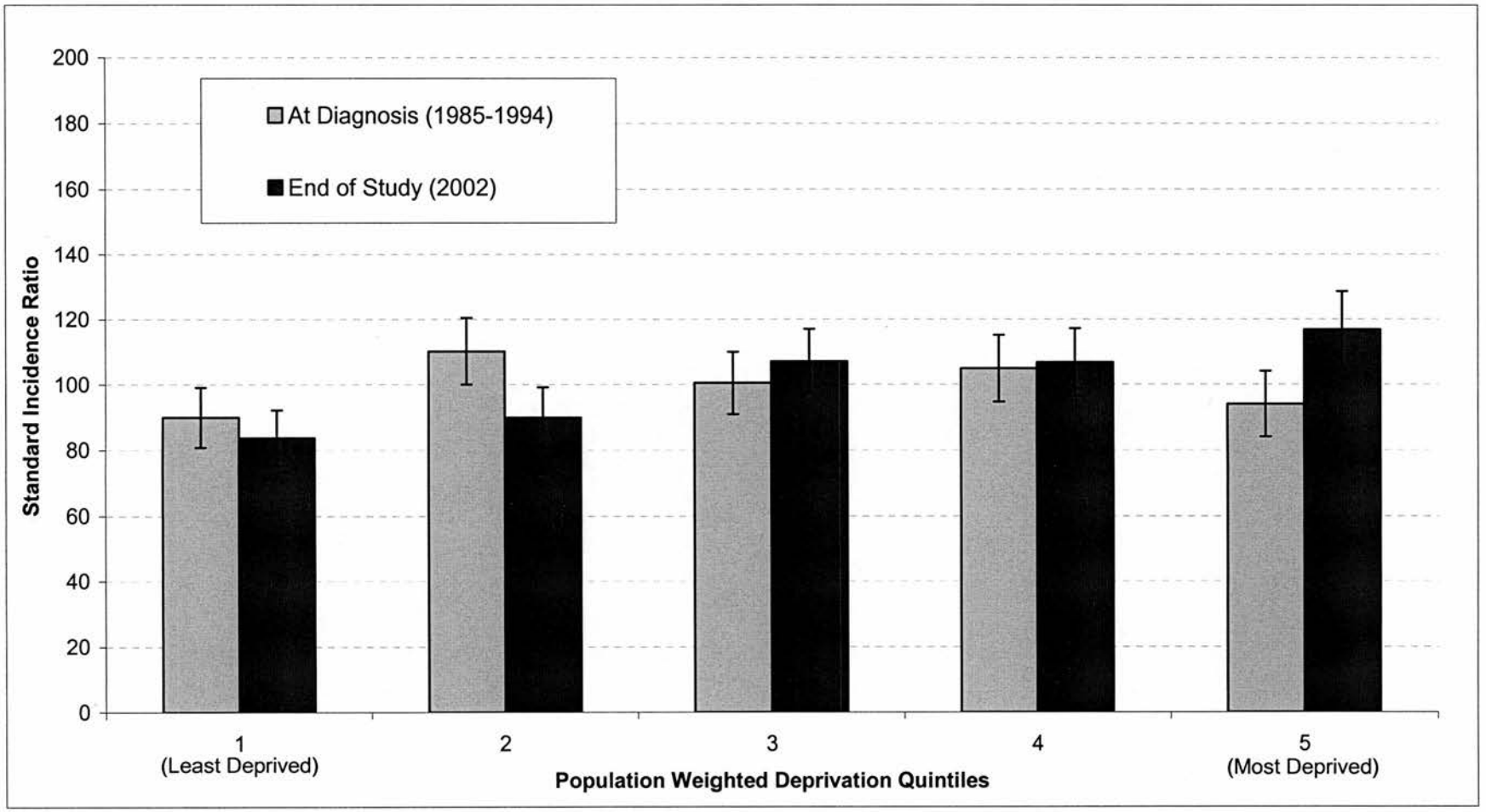


Figure 6.3 Standardised Incidence Ratios for Type 2 diabetes by deprivation at diagnosis and the end of the study period in Tayside, Scotland: surviving non-movers (bars are 95% confidence intervals).

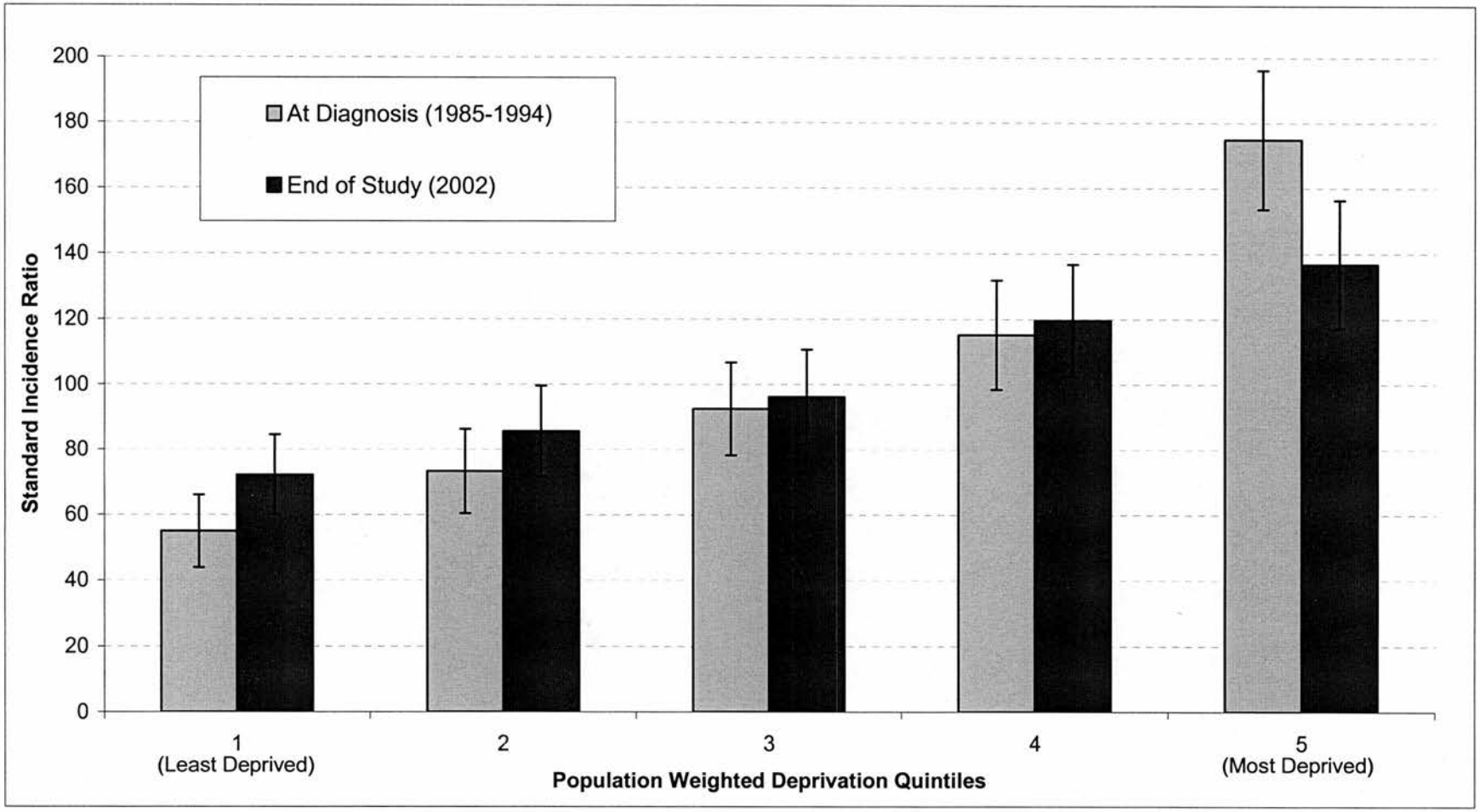


Figure 6.4 Standardised Incidence Ratios for Type 2 diabetes by deprivation at diagnosis and the end of the study period in Tayside, Scotland: surviving movers (bars are 95% confidence intervals).

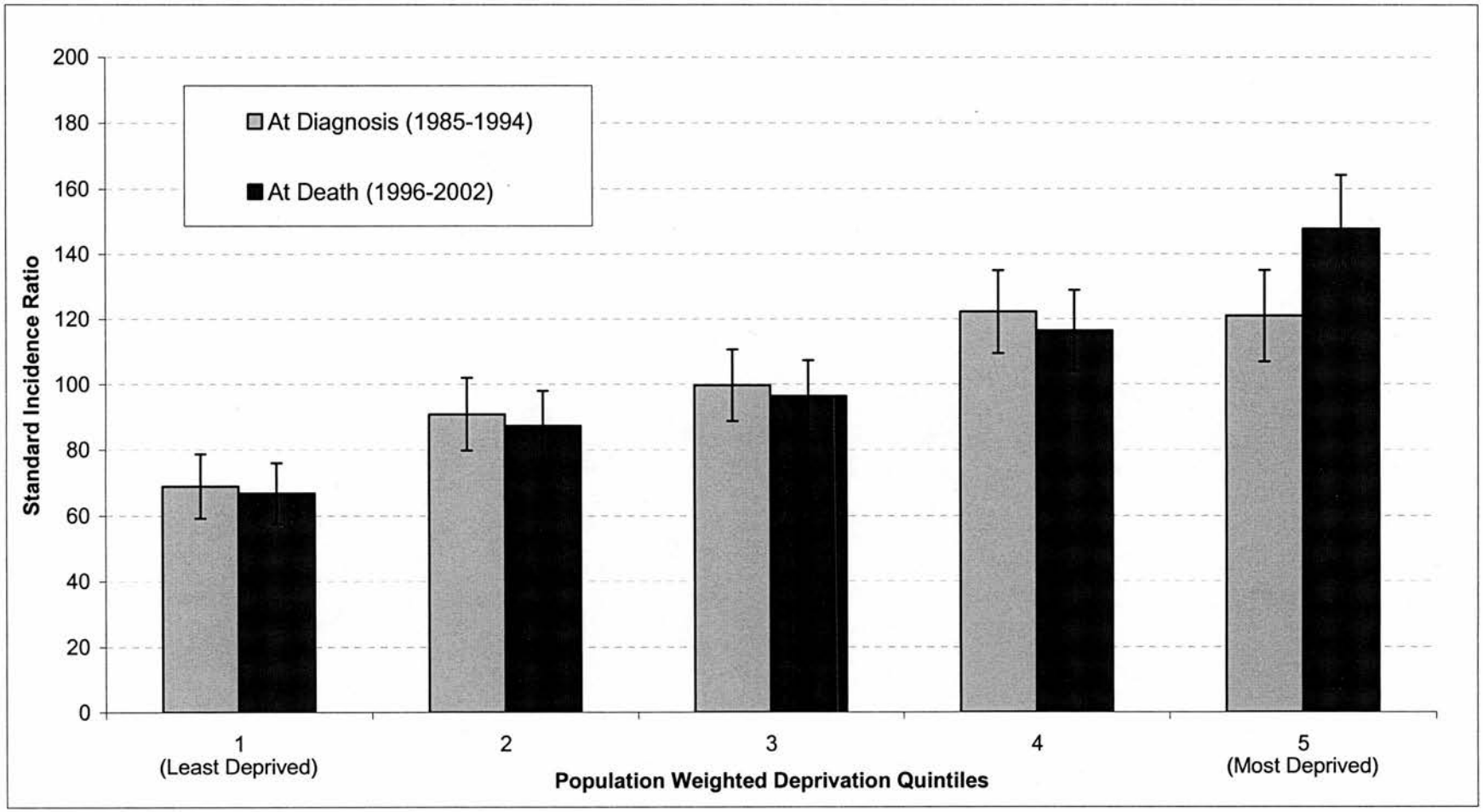


Figure 6.5 Standardised Incidence Ratios for people with Type 2 diabetes who died between 1996 and the end of the study period and deprivation in Tayside, Scotland: incidence and prevalence (bars are 95% confidence intervals).

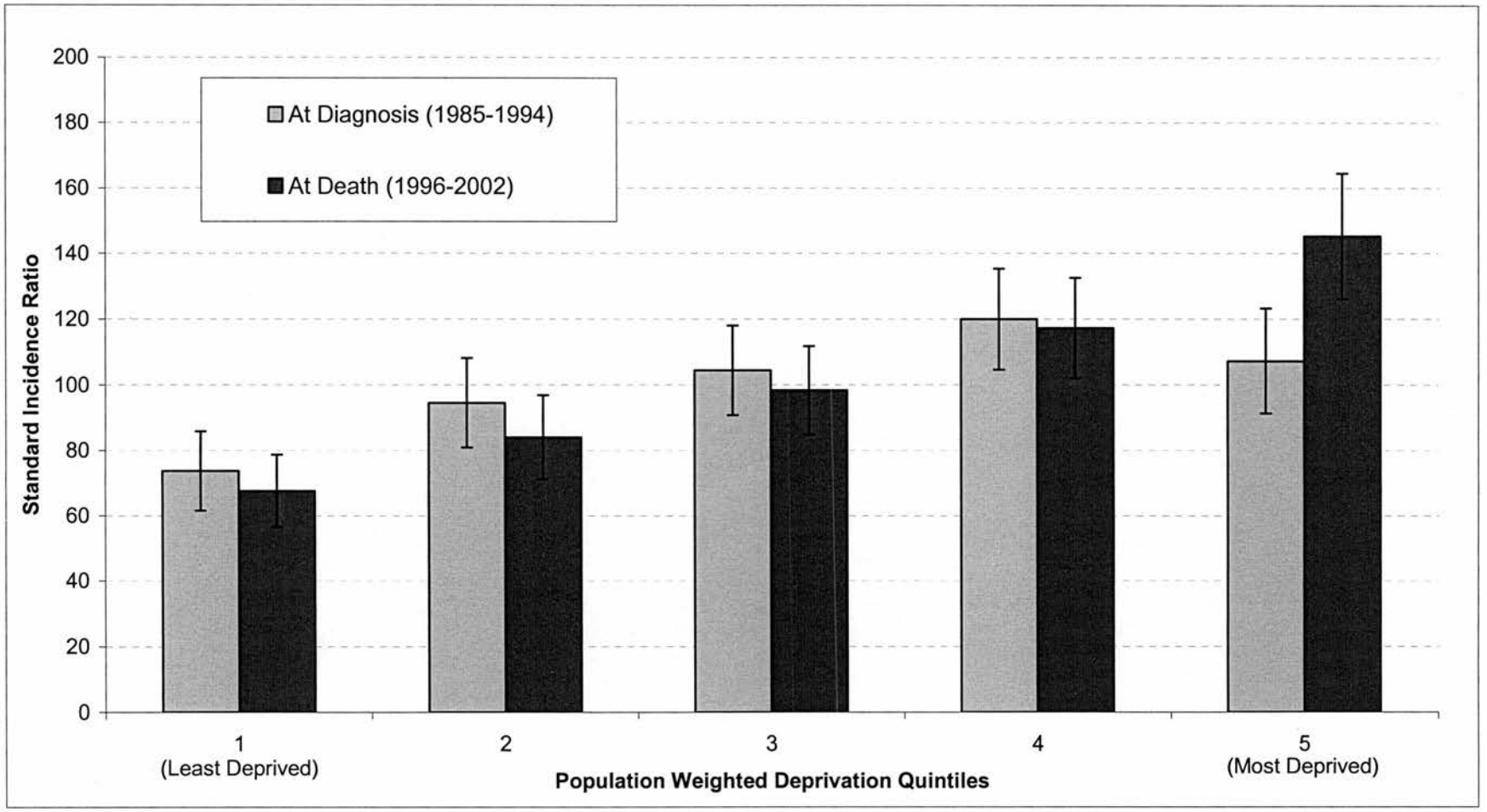


Figure 6.6 Standardised Incidence Ratios for people with Type 2 diabetes who died between 1996 and the end of the study period and deprivation in Tayside, Scotland: incidence and prevalence of non-movers (bars are 95% confidence intervals).

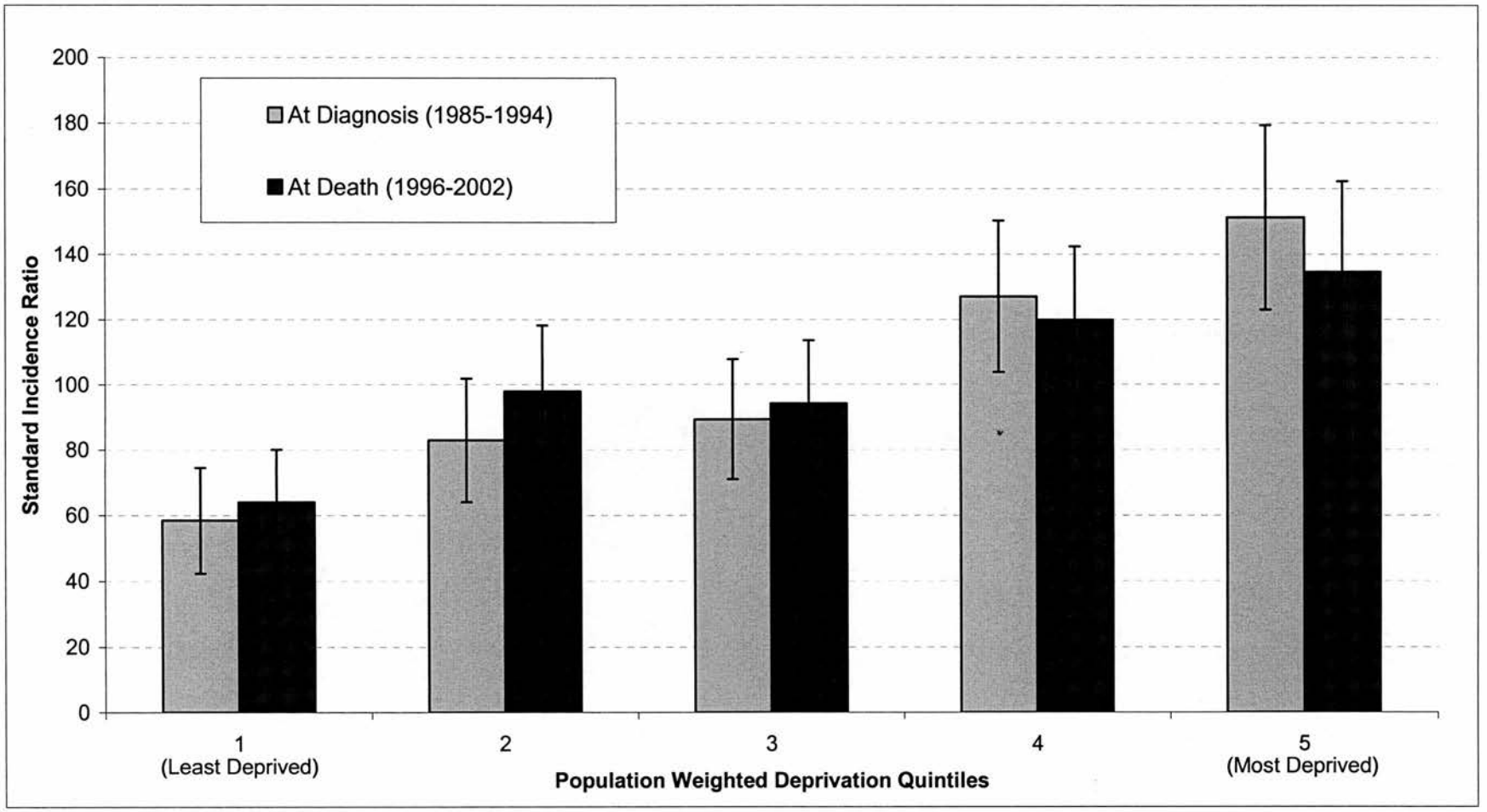


Figure 6.7 Standardised Incidence Ratios for people with Type 2 diabetes who died between 1996 and the end of the study period and deprivation in Tayside, Scotland: incidence and prevalence of movers (bars are 95% confidence intervals).

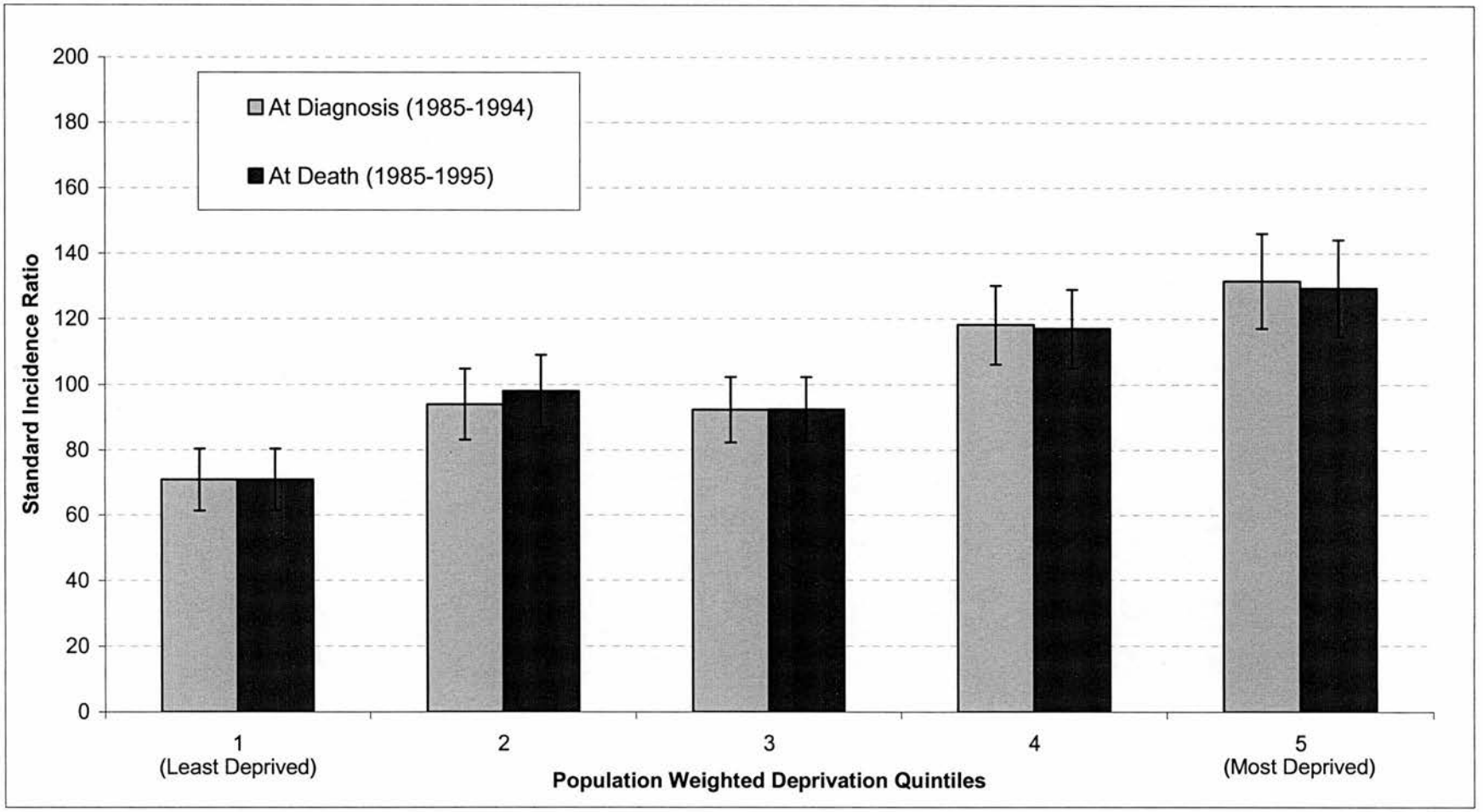


Figure 6.8 Standardised Incidence Ratios for people with Type 2 diabetes who died before 1996 and deprivation in Tayside, Scotland: incidence and prevalence (bars are 95% confidence intervals).

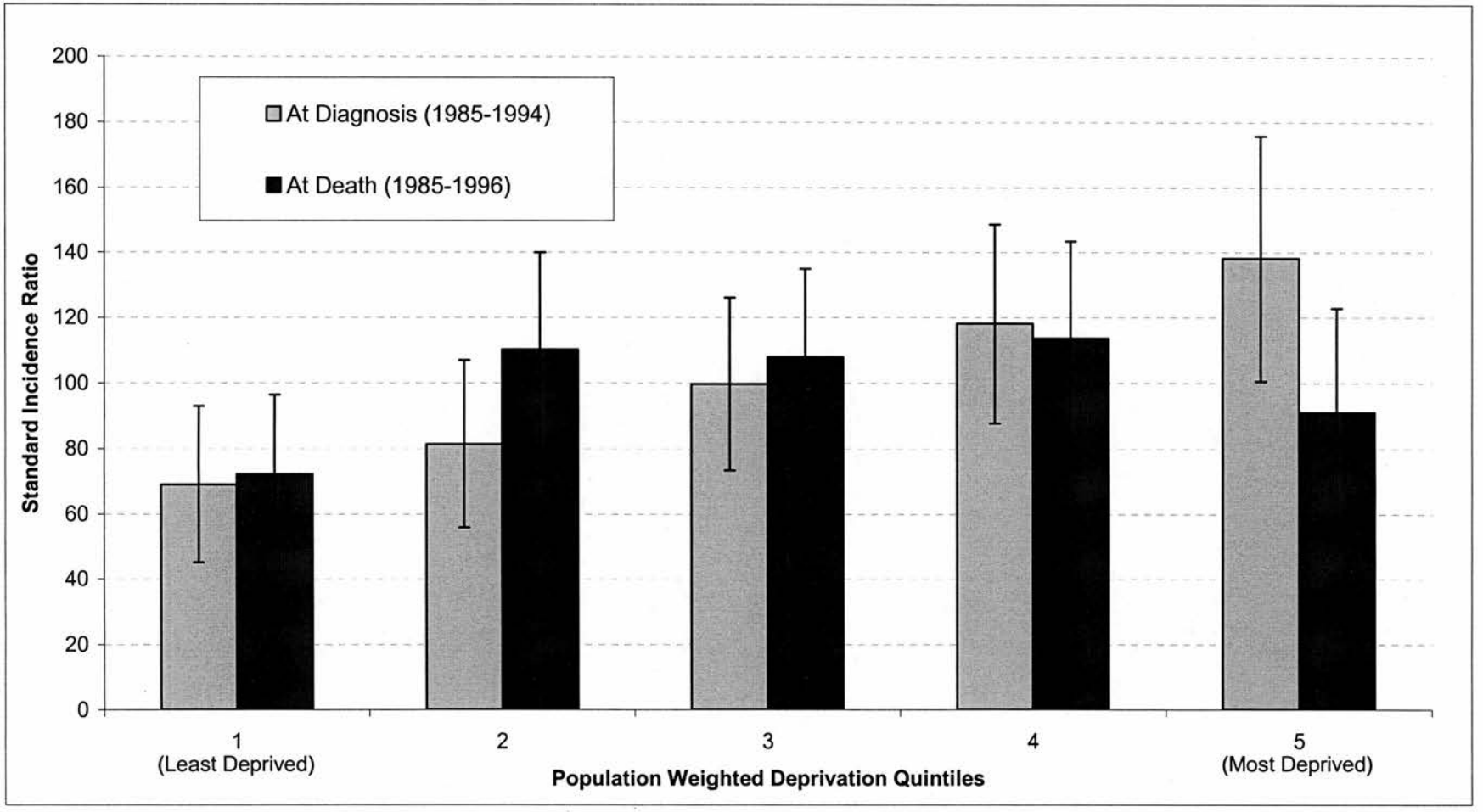


Figure 6.9 Standardised Incidence Ratios for people with Type 2 diabetes who died before 1996 and deprivation in Tayside, Scotland: incidence and prevalence of movers (bars are 95% confidence intervals).

CHAPTER 7 – [MANUSCRIPT 2] LOCALITY DEPRIVATION AND TYPE 2 DIABETES INCIDENCE IN TAYSIDE, SCOTLAND: A LOCAL TEST OF RELATIVE INEQUALITIES

Matthew Cox[1], Paul Boyle[1,2], Peter Davey[3], Zhiqiang Feng[1], Andrew Morris[4]

1 School of Geography & Geosciences, University of St Andrews, St Andrews, Scotland KY16 9AL

2 Social Dimensions of Health Institute, Universities of Dundee and St Andrews, Dundee, Scotland

3 Clinical Pharmacology & Therapeutics (MEMO Unit), Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY

4 DARTS/MEMO Collaboration, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY

Manuscript submitted to Social Science and Medicine for consideration for the special issue on 'Placing Health in Context.'

7.1 Abstract

There is increasing evidence that the socio-spatial context of the local area in which one lives can have an effect on health and we examine this in relation to the incidence of Type 2 diabetes. We test two opposing hypotheses which relate deprivation inequalities in neighbouring small areas to the incidence of Type 2 diabetes. First, the 'psycho-social hypothesis' suggests that negative comparisons made by individuals in relation to those who surround them may lead to chronic low-level stress via psycho-social pathways, the physiological effects of which may promote diabetes. Thus, we would expect people in deprived areas surrounded by less deprived areas would have an increased incidence of diabetes, compared to those in similarly deprived areas that are surrounded by equally or more deprived areas. Second, according to the 'pull-up/pull-down' hypothesis the social and environmental resources in the surrounding environment will influence circumstances in a particular area. Poorer areas surrounded by less deprived areas may benefit from better resources in the wider locality (pull-up) while less deprived areas surrounded by poorer areas may be hampered by the poorer resources available nearby (pull-down). To test these hypotheses we examine whether local-area deprivation inequality affects the incidence of Type 2 diabetes within Tayside, Scotland. Our results show deprivation was positively related to diabetes incidence ($p<0.001$), whilst deprivation inequality was negatively related ($p=0.006$). This suggests that diabetes is more common in deprived areas, but that deprived areas that were surrounded by relatively less deprived areas had lower diabetes incidence than would be expected from the deprivation score for that area. On the other hand, less deprived areas that were surrounded by relatively more deprived areas had higher

diabetes incidence. Our model results are consistent with a pull-up/pull-down model and lend no support to the 'psycho-social' model at this local scale of analysis.

Keywords Tayside, Scotland; Type 2 diabetes; deprivation; relative inequality; pull-up/pull-down hypothesis; psycho-social hypothesis.

7.2 Introduction

Type 2 diabetes occurs when the cells of the body become less sensitive to the action of the hormone insulin, when the body fails to produce enough insulin, or as is most often the case, as a combination of these two factors. Insulin is the key hormone involved with the storage and controlled release of the chemical energy available from food. Without insulin, glucose circulating in the blood is not taken up by the cells which results in a chronic state of hyperglycaemia (increased blood glucose). In the short term hyperglycaemia will manifest in extreme tiredness, weight loss, thirst and copious urination. However in the long term, hyperglycaemia results in micro- and macro-vascular damage and leads to a host of serious health problems including blindness, kidney failure, cardiovascular disease, and foot ulcers that if infected can lead to amputation. The prevalence of Type 2 diabetes is rising in the UK (Gatling, Budd, Walters et al., 1998; Harvey, Craney, & Kelly, 2002) and throughout the developed world (Amos, McCarty, & Zimmet, 1997; Passa, 2002; Wild, Roglic, Green et al., 2004) and has consequently become a key public health concern.

The underlying aetiology of Type 2 diabetes remains unclear, although the development of the condition has been shown to have a genetic component (Kaprio, Tuomilehto, Koskenvuo et al., 1992). Various individual risk factors have been identified, including poor diet and lack of exercise (UK Prospective Diabetes Study Group, 1988) and, as with many diseases, it is well established that the prevalence of Type 2 diabetes is related to material deprivation (Connolly, Unwin, Sherriff et al., 2000; Evans, Newton, Ruta et al., 2000; Meadows, 1995; Whitford, Griffin, & Prevost,

2003). More recently, and of particular relevance to this study, national-level analysis suggests that calorie consumption, obesity and diabetes mortality are positive related to income inequality in 21 developed nations (Pickett, Kelly, Brunner, Lobstein, & Wilkinson, 2005), and this suggests that there may be a relationship between the incidence of diabetes and the presence of socio-economic inequalities.

Our analysis in Tayside seeks, first, to examine whether the incidence (rather than prevalence) of Type 2 diabetes is related to deprivation and, second, whether variations in deprivation within the local context also influence the incidence of Type 2 diabetes. The premise is that the local 'socio-spatial' context of where one lives has a significant impact on health via a complex interplay of social, cultural and physical interactions which take place within and between local areas. Indeed, 'deprivation inequalities' within wards in England & Wales have previously been shown to be associated with limiting long term illness (Boyle, Gatrell, & Duke-Williams, 2004). This raises the intriguing question of whether living in a poor area surrounded by rich areas is better or worse for ones health than living in a poor area surrounded by similarly poor areas.

Of relevance to our analysis is the 'income inequality' debate. Income inequality refers to the difference in earnings between people at the top and bottom of society and this type of national-level measure has been associated with both mortality and morbidity outcomes (e.g. Kaplan, Pamuk, Lynch, Cohen, & Balfour, 1996; Kawachi, Kennedy, Lochner, & Prothrow-Stith, 1997; Ross, Wolfson, Dunn, Berthelot, Kaplan, & Lynch, 2000; Sanmartin, Ross, Tremblay, Wolfson, Dunn, & Lynch, 2003; Waldman, 1992; e.g. Wilkinson, 1992). Although this broad hypothesis has attracted considerable criticism (e.g. Deaton, 2003; Gravelle, Wildman, & Sutton, 2002), proponents of the income inequality thesis argue that it may be detrimental to health via key psycho-

social pathways associated with a person's standing in society, and has been used to explain why substantial health inequalities exist in developed nations despite the decline in absolute poverty that most have experienced. Wilkinson (1992; 1996; 1999), a key proponent of the income inequality thesis, believes that in the presence of such social inequalities, poorer people in developed societies compare themselves unfavourably with the rest of society and that this comparison is damaging to health. He argues that through the social tension and weak social affiliation that this may cause, individuals who perceive themselves as poor may experience chronic low-level stress as a result of the psycho-social impact of their relative social position. Such low-level stress may result in an unintentional physiological response, akin to flight-or-fight, which can affect a host of neuroendocrinic, physiological and immunological variables (Brunner, 1997). This thesis is particularly relevant to our study as over stimulation of the neuroendocrine pathways through chronic stress could well influence the development of Type 2 diabetes (Brunner & Marmot, 1999) as they play an important role in homeostasis and the mobilisation of energy within the body. It has also been suggested that, in addition to the physiological effects of stress, income inequality may also lead to sedentarism, increased calorie intake, and poor food choice, as the lack of control over one's life may lead to 'comfort' behaviours and an inability to affect positive lifestyle changes (Pickett, Kelly, Brunner et al., 2005). It therefore seems relevant to examine the role of relative inequalities in relation to diabetes incidence.

Most previous studies that have identified relationships between health outcomes and income inequality have been conducted for large geographical areas, such as nations (Wilkinson, 1996, American states Kennedy, Kawachi, & Prothrow-Stith, 1996), or metropolitan areas (Lynch, Kaplan, Pamuk, Cohen, Heck, Balfour et al., 1998).

Indeed, much of Wilkinson's argument rests on the comparisons that individuals are expected to make with the rest of society. However, it seems intuitively plausible that people's perception of their social status and position will also be formed in relation to those they live among in small neighbourhoods. Indeed, there is mounting evidence from multi-level analyses of the significant effect the socio-economic context of neighbourhood has on health outcomes (see Pickett & Pearl, 2001, for a review). Therefore it would seem entirely possible that the psycho-social factors implicated in the development of diabetes at the societal level may also have relevance in the local context – if people compare themselves to those in society in general, it would seem logical that they may also compare themselves to those who live around them, particularly if the circumstances of their neighbours are noticeably better or worse than their own.

In the absence of reliable income data collected for small areas[2], we therefore analyse 'relative deprivation inequality', and test the proposition that psycho-social factors are important at the local level, by assuming that those living in deprived areas that are surrounded by less deprived areas have a higher incidence of diabetes than would otherwise be expected. Similarly, those who live in less deprived areas that are surrounded by poorer areas may make positive comparisons and have lower levels of diabetes than would otherwise be expected. This is not a direct test of the income inequality thesis, but it does resonate with that research because of the focus on relative contexts and the influence that people's perceived standing in relation to others has on their health.

[2] The UK Census, which is the main source of reliable socio-economic data for small geographical areas, does not include an income question.

In contrast, however, we also consider a more materialistic interpretation of the effects of socio-economic inequalities on health. According to this alternative thesis, emphasis is given to the impact of poverty throughout the life-course of an individual and the associated under-investment within the areas in which they live. In this interpretation a person's material well-being and life opportunities, usually indicated by variables such as car ownership, home ownership and educational attainment, are held to be the critical factors underpinning health outcomes and they are expected to be far more influential than the possible psychological effects of relative social position within a social hierarchy (Shaw, Dorling, Gordon, & Davey Smith, 2004). From a geographical perspective, the areas in which poor people live have, in general, poorer physical, social and health infrastructures when compared to less deprived areas and this may be expected to have an effect on health (Macintyre, Ellaway, & Cummins, 2002). Building on such work, the 'pull-up/pull-down' hypothesis (Boyle, Gatrell, & Duke-Williams, 2004; Gatrell, 1997) suggests that the positive or negative social and environmental resources in the surrounding area will influence circumstances in a particular area of interest. For example, those living in a more deprived area that is surrounded by relatively less deprived areas may benefit from the better local services, recreation facilities and fresh food availability, allied with greater social regard for health promoting behaviours concerning diet, exercise and smoking in these neighbouring areas. This may lead to lower incidences of diabetes than would otherwise be expected ('pull-up'). On the other hand, the health of those in a less deprived area which is surrounded by more deprived areas may be negatively influenced by the social and environmental circumstances there ('pull-down'). In summary, the pull-up/pull-down and the psycho-social hypotheses would seem to predict opposing consequences for the geographical distribution of diabetes incidence resulting from the presence of relative socio-economic inequalities between nearby

small areas. By examining relative deprivation inequality (the difference in deprivation between an area and surrounding nearby areas) in Tayside, we can assess whether there is any evidence of either a pull-up/pull-down effect or for the importance of psycho-social factors on the incidence of diabetes.

7.3 Method

We collected information from the DARTS database (Morris, Boyle, MacAlpine et al., 1997) on the 3917 people in Tayside with a date of diagnosis for Type 2 diabetes recorded between the 1st January 1998 and the 31st December 2001. For each case we know the age, sex and residential location. These cases were distributed across 3382 Output Areas (the smallest areas used for the dissemination of the 2001 Census data in Scotland). Rates were highest in the smaller urban areas, which tend to be more deprived, and lower in more rural areas.

We modelled the distribution of cases in five age (0-44 yrs; 45-54 yrs; 55-64 yrs; 65-74 yrs; 75+ yrs) and sex groups, giving 33820 observations, using negative binomial regression with the significance level set *a priori* at $p<0.05$. The age- and sex-specific denominator populations for the Output Areas were extracted from the 2001 Census. The natural log of the age- and sex-specific population was included as an offset to account for the expected increase in the number of cases with the population size of the Output Area.

A series of independent variables were modelled separately and then in combination. The age and sex variables were the only explanatory variables which were available for

the individual cases from the DARTS data; the remaining variables were all ecological, having been extracted for Output Areas from the 2001 Census data. These included the % of non-white residents in the Output Area, the population density of the Output Area and a series of variables which are typically used to measure deprivation. These were the % of residents in households with no car; the residents in households with 1 or more persons per room as a % of all residents in households (overcrowding); the % of residents in households with head of household in social class IV and V; and unemployed male residents aged over 16 as a proportion of all residents aged over 16. The Carstairs Deprivation Index (Carstairs & Morris, 1991), which is a composite variable based on the four variables described above, was also included and is mapped in Figure 7.1. The most deprived Output Areas are in Dundee, which is the largest city in Tayside.

Importantly, we also included a measure of deprivation inequality which compared the Carstairs deprivation score in each area with the deprivation scores in the surrounding areas. Rather than simply comparing the deprivation score for each area and its adjacent neighbours, we used a gravity model approach to weight surrounding scores for each target area. In each gravity model, the 'influence' of every Output Area, in or within 20km of Tayside (to negate potential border effects), on the target Output Area was measured as a function of its population size and the square of the distance between its population-weighted centroid and that for the target area. The influence of each area was determined by:

$$I_{ij} = \frac{P_i * P_j}{D_{ij}^{\ 2}}$$

Where:

I_{ij} denotes the influence of OA_i on OA_j

P_i denotes the population of OA_i

P_j denotes the population of OA_j

D_{ij}^2 denotes the distance squared between OA_i and OA_j

The influence of each Output Area was then measured by dividing population by distance squared to give a weight, which was further divided by the sum of the weights so that the final weights for all the areas combined summed to one. By applying these weights to their respective Output Area deprivation score and then summing the scores, we are left with an overall locality deprivation score, whereby the Output Areas with the greatest weight (being close to the target area, or having a large population) had the greatest input[3]. Thus, to derive the average deprivation score for the target OA (A_i) from the surrounding areas we calculated:

$$A_i = \frac{\sum_j^k C_j * I_{ij}}{\sum_j^k I_{ij}}$$

Where:

C_j is Carstairs deprivation score at OA_j and k is the number of surrounding OAs.

[3] In addition, we explored whether raising distance to different powers (steepening the distance decay effect) influenced the results, although none improved the fit more than using distance squared.

To derive deprivation inequality we then subtracted the relevant locality deprivation score from the Output Area deprivation score of the area of interest. If the Output Area was more deprived than its surrounds then deprivation inequality is positive: if the area was less deprived the variable is negative.

This relative deprivation index provides a useful comparative variable which is genuinely 'contextual'. Many studies have used deprivation scores to reflect 'context'. However, as Graham, Boyle, Curtis, & Moore (2004) argue, these scores are, of course, derived from the characteristics of the individuals who live in these places (see also Greenland, 2001). They are not strictly 'contextual' in the sense that environmental measures of pollution, or accessibility to health care would be (Macintyre, Ellaway, & Cummins, 2002) and it is not easy to determine whether any relationship between deprivation and health represents the socio-economic 'composition' of individuals in an area or the socio-economic 'context' of that area. Whether deprivation should be treated as a contextual variable is, therefore, debateable. However, the relative deprivation variable that we use here – the difference in deprivation between an area and surrounding nearby areas – certainly is contextual, as it compares the relative circumstances of each place and its surrounds.

7.4 Results

The results of a series of univariate negative binomial regression models for Type 2 diabetes incidence are shown in Table 7.1. As expected, females were less likely to be diagnosed with diabetes ($p<0.001$) and the incidence of Type 2 diabetes increased significantly with age ($p<0.001$). Diabetes was also positively and significantly related

to some of the socio-economic characteristics of the Output Area including the % of residents in households with no car ($p<0.001$), the % of residents in households with head of household in social class IV and V ($p<0.001$), unemployed male residents aged over 16 as a proportion of all residents aged over 16 ($p<0.001$), and Carstairs deprivation ($p<0.001$). However, there was no significant association with the % of households that were overcrowded, the % of non-white residents, or population density. Deprivation inequality was positively and highly significantly associated with the incidence of Type 2 diabetes.

The results from the independent variables fitted in a multivariate regression revealed an important difference to the univariate analysis (Table 7.2). Age ($p<0.001$) and sex ($p<0.001$) remained significant, and area deprivation ($p<0.001$) and deprivation inequality ($p=0.006$) also remained significant. However, after allowing for age, sex and, most importantly, area deprivation, the relationship between Type 2 diabetes incidence and deprivation inequality became negative. This suggests that, having controlled for area deprivation, areas surrounded by relatively less deprived areas had lower Type 2 diabetes incidence than would otherwise be expected, whereas areas surrounded by relatively more deprived areas had a higher incidence of Type 2 diabetes than would otherwise be expected.

7.5 Discussion

We have examined how the relative deprivation circumstances of small areas are related to Type 2 diabetes and proposed two competing hypotheses. First, the 'psycho-social hypothesis' would suggest that those in deprived areas, who were surrounded by

areas that were relatively less deprived, would have poorer health than expected from the deprivation circumstances of the area in which they lived. This hypothesis builds on the work of Wilkinson and others, who argue that income inequality within societies influences the health of the worse off via the psychological and emotional impact of living in those circumstances. Wilkinson (2006), in his most recent volume, suggests that the most important psychosocial risk factors associated with inequality are low social status, weak friendship networks, and the poor quality of early childhood experience, whilst chronic stress has been put forward as the biological mechanism by which these risk factors affect health:

> *"Psychosocial factors, many of which are associated with low social status, are known to affect health partly through direct physiological effects of chronic stress... and partly through their influence on health related behaviour... Others have argued that low social status is stressful because people are made to feel looked down on, devalued and inferior."* (Wilkinson & Pickett, 2006, p.1178)

Our study explores similar issues within and between small geographical areas, although we use measures of deprivation, rather than income inequality. Wilkinson & Pickett (2006), and others (Franzini, Ribble, & Spears, 2001; Hsieh & Pugh, 1993; Subramanian & Kawachi, 2004), have reported that income inequality appears to be more strongly associated with health when measured at the national, or possibly regional, level, but less convincingly at the local level. According to Wilkinson & Pickett (2006, p.1774), this is because:

> *"income inequality in small areas is affected by the degree of residential segregation of rich and poor and that the health of people in deprived neighbourhoods is poorer not because of the inequality within their neighbourhoods, but because they are deprived in relation to the wider society. If that is what matters, then it is to be expected that inequality will only be sensitive to this broader pattern of deprivation if inequality is measured across the wider framework in which the relevant social comparisons are made. The fact that measures of inequality made across larger areas are more closely related to health bears out this point."*

They go on to explain that:

> *"The lower class identity of people in a poor neighbourhood is inevitably defined in relation to a hierarchy which includes a knowledge of the existence of superior classes who may live in other areas some distance away."* (Wilkinson & Pickett, 2006, p.1774)

We find the focus on comparisons at the societal level overstated. Indeed, Wilkinson & Picket acknowledge that the hierarchy which defines people's identities *includes* knowledge of superior classes who live elsewhere, implying that they will also be shaped by more local comparisons. And as Wilkinson (2006) recently put it:

> *"Perhaps the underlying message is that the most widespread and potent kind of stress in modern societies centres on our anxieties about how others see us, on our self-doubts and social insecurities. As social beings, we continuously monitor how others respond to us, so much so that it is sometimes as if we*

> *experienced ourselves through each other's eyes. Shame and embarrassment have been called the social emotions as they shape our behaviour to meet acceptable standards and spare us from the stomach-tightening we feel when we have made fools of ourselves in front of others... It appears that it is also how society gets under the skin to affect health."*

If people are expected to make comparisons with others in society, the results of which are so powerful as to have implications for their mental and physical health, it seems unreasonable to assume that people would not also make comparisons between themselves and those who live around them. In Britain at least, neighbourly comparisons with 'the Joneses' are a well-known feature of suburban life. And there are numerous examples in the geographical literature which indicate that people's behaviours are likely to be influenced by those who live around them. We know that people tend to live close to others with similar characteristics and that outcomes such as self-rated health (Bowling, Barber, Morris, & Ebrahim, 2006; Stafford, Martikainen, Lahelma, & Marmot, 2004; Wen, Browning, & Cagney, 2003), cardio-vascular disease (Borrell, Diez Roux, Rose, Catellier, & Clark, 2004; Davey Smith, Hart, Watt, Hole, & Hawthorne, 1998) and even fertility behaviour may be strongly associated with the context within which people reside. Szreter (1996, p.546), for example, puts this clearly when discussing historical variations in fertility patterns:

> *"It is because fertility change was mediated by shifting roles and norms that it principally occurred not to whole social classes or to individual occupations but to social groups and communities. This is because roles, norms and social identities are essential elements of the shared language of any mutually recognising, communicating human group. They are constructed by and*

> *embodied in the shared social practices and values of social groups or what might more accurately be termed 'communication communities'."*

It would seem quite reasonable to suppose for those who do make comparisons with others, they are just as likely to compare themselves to those in the local neighbourhood, as to those in society more generally. If perceived relative inequality is an important determinant of health, surely it is hard to imagine that positive or negative *local* comparisons would not also impact on health – indeed, it seems to us that such local comparisons are likely to be at least as informed and meaningful to most people as comparisons with 'society in general'. Thus, we take the view that local comparisons will be made – whether they are likely to influence health more than more materialistic concerns is, of course, debateable.

Our second, and opposing, 'pull up/pull down hypothesis' is a more materialistic interpretation of the effects of socio-economic inequalities on health, which is concerned with poverty and the likely resources available to people within the areas in which they live. A person's material well-being and life opportunities are held to be the critical factors underpinning health outcomes and they are expected by many to be far more influential than the possible psychological effects of relative social position within a social hierarchy (Shaw, Dorling, Gordon et al., 2004). Thus, according to Stafford & Marmot (2003, pp.357-8):

> *"In a 'collective resources model', people in non-deprived areas have better health than people in deprived areas because there are more collective resources (including material and social resources, such as services, job opportunities, and social supports). The ability of wealthier, more powerful*

> *individuals to attract high quality amenities and services enhances the area for all residents. The beneficial effect of living in an area with greater collective resources may be greater for poorer individuals; they may be less able to purchase goods and services privately and may be more dependent on locally provided facilities."*

We extend this line of reasoning, which focused on comparing health outcomes for individuals living in areas with different levels of deprivation. According to our hypothesis, we argue that understanding the role of local circumstances, or 'collective resources', on people's health need not focus entirely on the characteristics of the small, arbitrary administrative area that they happen to reside in. Instead, we argue that the context surrounding these areas is likely to be influential, particularly in those places that are surrounded by areas that are relatively dissimilar to the one they live in.

Thus, we explored local relative inequalities by comparing the deprivation circumstances between the place of residence and the wider locality in which people lived in each small area within Tayside using a gravity model method. We then compared this variable to the incidence of Type 2 diabetes. Our empirical results suggest that, controlling for the deprivation of the area of residence, deprivation inequality between small areas is significantly related to an increased incidence of Type 2 diabetes. In Tayside, areas that are surrounded by relatively less deprived areas have lower incidence of Type 2 diabetes, whereas areas surrounded by more deprived areas have a higher incidence. These results are compatible with the pull-up/pull-down hypothesis, rather than the psycho-social hypothesis and, although based on a different type of analysis, they would seem to support the analysis of Stafford & Marmot (2003,

p.357) who could find: "no evidence that personal poverty combined with affluent neighbourhood had negative health consequences."

A small number of previous studies have also found relationships between health and deprivation inequality. Ben-Shlomo, White, & Marmot (1996) reported a relationship between deprivation inequality and mortality for (the relatively large) English local authorities. Meanwhile, Boyle, Gatrell, & Duke-Williams (1999; 2004) found relationships between deprivation variability and both standardised morbidity ratios and the reporting of limiting long-term illness, in Census Wards in England and Wales. This study improves on that work by: focusing on a single, diagnosed medical condition; employing a more accurate and versatile measure of deprivation inequality based on a gravity model approach which compares deprivation between places, rather than simply considering the variability in deprivation within places; and using a measure of deprivation that is inherently 'contextual'.

At present there is no clear evidence as to what size of area is most poignant for studying the effects of local area context on health and many studies employ geographical units based on arbitrary administrative boundaries defined by the Census. By including the relative deprivation characteristics of surrounding areas, weighted by population and distance, we have introduced a broader concept of context. We have shown that deprivation inequality between an Output Area and its neighbours has a significant impact on diabetes incidence. The results suggest that while the deprivation of the area in which people live is important, resources in the wider locality are also influential.

Our study is not without problems. The lack of data on individuals is a particular problem, as it would be useful to control for individual circumstances before assessing the impact of the local context. However, since our focus was on small-area effects, it was not possible to find the micro-data on people with diabetes that would allow us to explore these. We should also acknowledge, of course, that while our analysis focuses specifically on the comparisons between small places – a measure of relative inequality – we have certainly not tested Wilkinson's hypothesis directly, as his arguments relate to *income*, rather than deprivation, inequality. Even so, the theoretical underpinning of Wilkinson's thesis is still relevant, as the processes he describes encourage us to explore how people's perceptions of their position may be influenced by context, be it local or national. Overall, our results suggest that 'collective resources' in the local area are likely to have more impact on health than negative psycho-social comparisons and this has broad public health implications, particularly in relation to neighbourhood planning and segregation issues.

7.6 References

Amos, A.F., McCarty, D.J., & Zimmet, P. (1997). The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. *Diabetic Medicine*, 14(12), S7-S85.

Ben-Shlomo, Y., White, I.R., & Marmot, M. (1996). Does the variation in the socioeconomic characteristics of an area affect mortality? *Bmj*, 312(7037), 1013-1014.

Borrell, L.N., Diez Roux, A.V., Rose, K., Catellier, D., & Clark, B.L. (2004). Neighbourhood characteristics and mortality in the Atherosclerosis Risk in Communities Study. *Int J Epidemiol*, 33(2), 398-407.

Bowling, A., Barber, J., Morris, R., & Ebrahim, S. (2006). Do perceptions of neighbourhood environment influence health? Baseline findings from a British survey of aging. *J Epidemiol Community Health*, 60(6), 476-483.

Boyle, P.J., Gatrell, A.C., & Duke-Williams, O. (1999). The effect on morbidity of variability in deprivation and population stability in England and Wales: an investigation at small-area level. *Soc Sci Med*, 49(6), 791-799.

Boyle, P.J., Gatrell, A.C., & Duke-Williams, O. (2004). Limiting Long-term Illness and Locality Deprivation in England and Wales: Acknowledging the 'Socio-spatial Context. In P. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geographies of Health Inequality in the Developed World* (pp. 293-308): Ashgate.

Brunner, E. (1997). Socioeconomic determinants of health - Stress and the biology of inequality. *British Medical Journal*, 314(7092), 1472-1476.

Brunner, E., & Marmot, M. (1999). Social organisation, stress, and health. In M. Marmot, & R.G. Wilkinson (Eds.), *Social determinants of Health* (pp. 17-43): Oxford University Press.

Carstairs, V., & Morris, R. (1991). *Deprivation and Health in Scotland*: Aberdeen University Press

Connolly, V., Unwin, N., Sherriff, P., Bilous, R., & Kelly, W. (2000). Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of Type 2 diabetes mellitus in deprived areas. *Journal of Epidemiology and Community Health*, 54(3), 173-177.

Davey Smith, G., Hart, C., Watt, G., Hole, D., & Hawthorne, V. (1998). Individual social class, area-based deprivation, cardiovascular disease risk factors, and mortality: the Renfrew and Paisley Study. *J Epidemiol Community Health*, 52(6), 399-405.

Deaton, A. (2003). Health, inequality, and economic development. *Journal of Economic Literature*, 41(1), 113-158.

Evans, J.M.M., Newton, R.W., Ruta, D.A., MacDonald, T.M., & Morris, A.D. (2000). Socio-economic status, obesity and prevalence of Type 1 and Type 2 diabetes mellitus. *Diabetic Medicine*, 17(6), 478-480.

Franzini, L., Ribble, J., & Spears, W. (2001). The effects of income inequality and income level on mortality vary by population size in Texas counties. *J Health Soc Behav*, 42(4), 373-387.

Gatling, W., Budd, S., Walters, D., Mullee, M.A., Goddard, J.R., & Hill, R.D. (1998). Evidence of an increasing prevalence of diagnosed diabetes mellitus in the Poole area from 1983 to 1996. *Diabetic Medicine*, 15(12), 1015-1021.

Gatrell, A.C. (1997). Structures of geographical and social space and their consequences for human health. *Geografiska Annaler, Series B: Human Geography*, 79(3), 141-154.

Graham, E., Boyle, P.J., Curtis, S., & Moore, E. (2004). Does place matter in studies of health inequalities? In P.J. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geography of Health Inequalities: Views from Britain and North America.* London: Ashgate.

Gravelle, H., Wildman, J., & Sutton, M. (2002). Income, income inequality and health: what can we learn from aggregate data? *Social Science & Medicine*, 54(4), 577-589.

Greenland, S. (2001). Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. *International Journal of Epidemiology*, 30(6), 1343-1350.

Harvey, J.N., Craney, L., & Kelly, D. (2002). Estimation of the prevalence of diagnosed diabetes from primary care and secondary care source data: comparison of record linkage with capture-recapture analysis. *J Epidemiol Community Health*, 56(1), 18-23.

Hsieh, C.C., & Pugh, M.D. (1993). Poverty, income inequality, and violent crime: a meta-analysis of recent aggregate data studies. *Criminal Justice Review*, 18, 182-202.

Kaplan, G.A., Pamuk, E.R., Lynch, J.W., Cohen, R.D., & Balfour, J.L. (1996). Inequality in income and mortality in the United States: Analysis of mortality and potential pathways. *British Medical Journal*, 312(7037), 999-1003.

Kaprio, J., Tuomilehto, J., Koskenvuo, M., Romanov, K., Reunanen, A., Eriksson, J., Stengard, J., & Kesaniemi, Y.A. (1992). Concordance for Type-1 (Insulin-Dependent) and Type-2 (Non-Insulin-Dependent) Diabetes-Mellitus in a Population-Based Cohort of Twins in Finland. *Diabetologia*, 35(11), 1060-1067.

Kawachi, I., Kennedy, B.P., Lochner, K., & Prothrow-Stith, D. (1997). Social capital, income inequality, and mortality. *Am J Public Health*, 87(9), 1491-1498.

Kennedy, B.P., Kawachi, I., & Prothrow-Stith, D. (1996). Income distribution and mortality: cross sectional ecological study of the Robin Hood index in the United States. *Bmj*, 312(7037), 1004-1007.

Lynch, J.W., Kaplan, G.A., Pamuk, E.R., Cohen, R.D., Heck, K.E., Balfour, J.L., & Yen, I.H. (1998). Income inequality and mortality in metropolitan areas of the United States. *American Journal of Public Health*, 88(7), 1074-1080.

Macintyre, S., Ellaway, A., & Cummins, S. (2002). Place effects on health: how can we conceptualise, operationalise and measure them? *Social Science & Medicine*, 55(1), 125-139.

Meadows, P. (1995). Variation of Diabetes-Mellitus Prevalence in General-Practice and Its Relation to Deprivation. *Diabetic Medicine*, 12(8), 696-700.

Morris, A.D., Boyle, D.I.R., MacAlpine, R., EmslieSmith, A., Jung, R.T., Newton, R.W., & MacDonald, T.M. (1997). The diabetes audit and research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. *British Medical Journal*, 315(7107), 524-528.

Passa, P. (2002). Diabetes trends in Europe. *Diabetes-Metabolism Research and Reviews*, 18, S3-S8.

Pickett, K.E., & Pearl, M. (2001). Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. *J Epidemiol Community Health*, 55(2), 111-122.

Pickett, K.E., Kelly, S., Brunner, E., Lobstein, T., & Wilkinson, R.G. (2005). Wider income gaps, wider waistbands? An ecological study of obesity and income inequality. *J Epidemiol Community Health*, 59(8), 670-674.

Ross, N.A., Wolfson, M.C., Dunn, J.R., Berthelot, J.M., Kaplan, G.A., & Lynch, J.W. (2000). Relation between income inequality and mortality in Canada and in the United States: cross sectional assessment using census data and vital statistics. *Bmj*, 320(7239), 898-902.

Sanmartin, C., Ross, N.A., Tremblay, S., Wolfson, M., Dunn, J.R., & Lynch, J. (2003). Labour market income inequality and mortality in North American metropolitan areas. *J Epidemiol Community Health*, 57(10), 792-797.

Shaw, M., Dorling, D., Gordon, D., & Davey Smith, G. (2004). The widening gap - health inequalities in Britain at the end of the twentieth century. In P.J. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geographies of Health Inequalities in the Developed World* (pp. pp. 77-100). London: Ashgate.

Stafford, M., & Marmot, M. (2003). Neighbourhood deprivation and health: does it affect us all equally? *Int J Epidemiol*, 32(3), 357-366.

Stafford, M., Martikainen, P., Lahelma, E., & Marmot, M. (2004). Neighbourhoods and self rated health: a comparison of public sector employees in London and Helsinki. *J Epidemiol Community Health*, 58(9), 772-778.

Subramanian, S.V., & Kawachi, I. (2004). Income inequality and health: what have we learned so far? *Epidemiol Rev*, 26, 78-91.

Szreter, S. (1996). *Fertility, Class and Gender on Britain 1860-1940* Cambridge: Cambridge University Press

UK Prospective Diabetes Study (1988). UK Prospective Diabetes Study. IV. Characteristics of newly presenting Type 2 diabetic patients: male preponderance and obesity at different ages. Multi-center Study. *Diabet Med*, 5(2), 154-159.

Waldman, R.J. (1992). Income distribution and child mortality. *Quarterly journal of Economics*, 107, 1283-1302.

Wen, M., Browning, C.R., & Cagney, K.A. (2003). Poverty, affluence, and income inequality: neighborhood economic structure and its implications for health. *Soc Sci Med*, 57(5), 843-860.

Whitford, D.L., Griffin, S.J., & Prevost, A.T. (2003). Influences on the variation in prevalence of Type 2 diabetes between general practices: practice, patient or socioeconomic factors? *British Journal of General Practice*, 53(486), 9-14.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes - Estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(5), 1047-1053.

Wilkinson, R.G. (1992). For Debate - Income-Distribution and Life Expectancy. *British Medical Journal*, 304(6820), 165-168.

Wilkinson, R.G. (1996). *Unhealthy Societies: the Affliction of Inequality* London: Routledge

Wilkinson, R.G. (1999). Putting the picture together: prosperity, redistribution health and welfare. In M. Marmot, & R.G. Wilkinson (Eds.), *Social determinants of Health* (pp. 256-274): Oxford University Press.

Wilkinson, R.G. (2006). The Impact of Inequality: Empirical Evidence. *Renewal*, 14.

Wilkinson, R.G., & Pickett, K.E. (2006). Income inequality and population health: a review and explanation of the evidence. *Soc Sci Med*, 62(7), 1768-1784.

7.7 Tables & figures

Variable	Parameter estimate	Standard error	p-value
Age			
45-54	2.049512	0.0661572	<0.001
55-64	2.678852	0.061982	<0.001
65-74	2.938581	0.0612284	<0.001
75+	2.574394	0.0662146	<0.001
Sex (female)	-0.2867863	0.0412582	<0.001
% households no car	0.0082165	<0.0019395	<0.001
% households overcrowded	0.0159351	0.0090818	0.079
% low social class	0.0146561	0.0026629	<0.001
% non white ethnic group	-0.0087938	0.0060636	0.147
% unemployment	0.0113572	0.0028155	<0.001
Carstairs area deprivation	0.0522753	0.0076443	<0.001
Deprivation inequality	0.0501347	0.0109731	<0.001
Population Density	-1.27E-08	7.98E-07	0.987

Table 7.1 Type 2 diabetes incidence (univariate models)

Variable	Parameter estimate	Standard error	p-value
Age			
45-54	2.090241	0.0660653	<0.001
55-64	2.719943	0.0618786	<0.001
65-74	2.987469	0.0611352	<0.001
75+	2.653115	0.0661805	<0.001
Sex (female)	-0.3265832	0.0325839	<0.001
Carstairs area deprivation	0.0879695	0.0098484	<0.001
Deprivation inequality	-0.0387508	0.0141039	0.006

Table 7.2 Type 2 diabetes incidence (multivariate model)

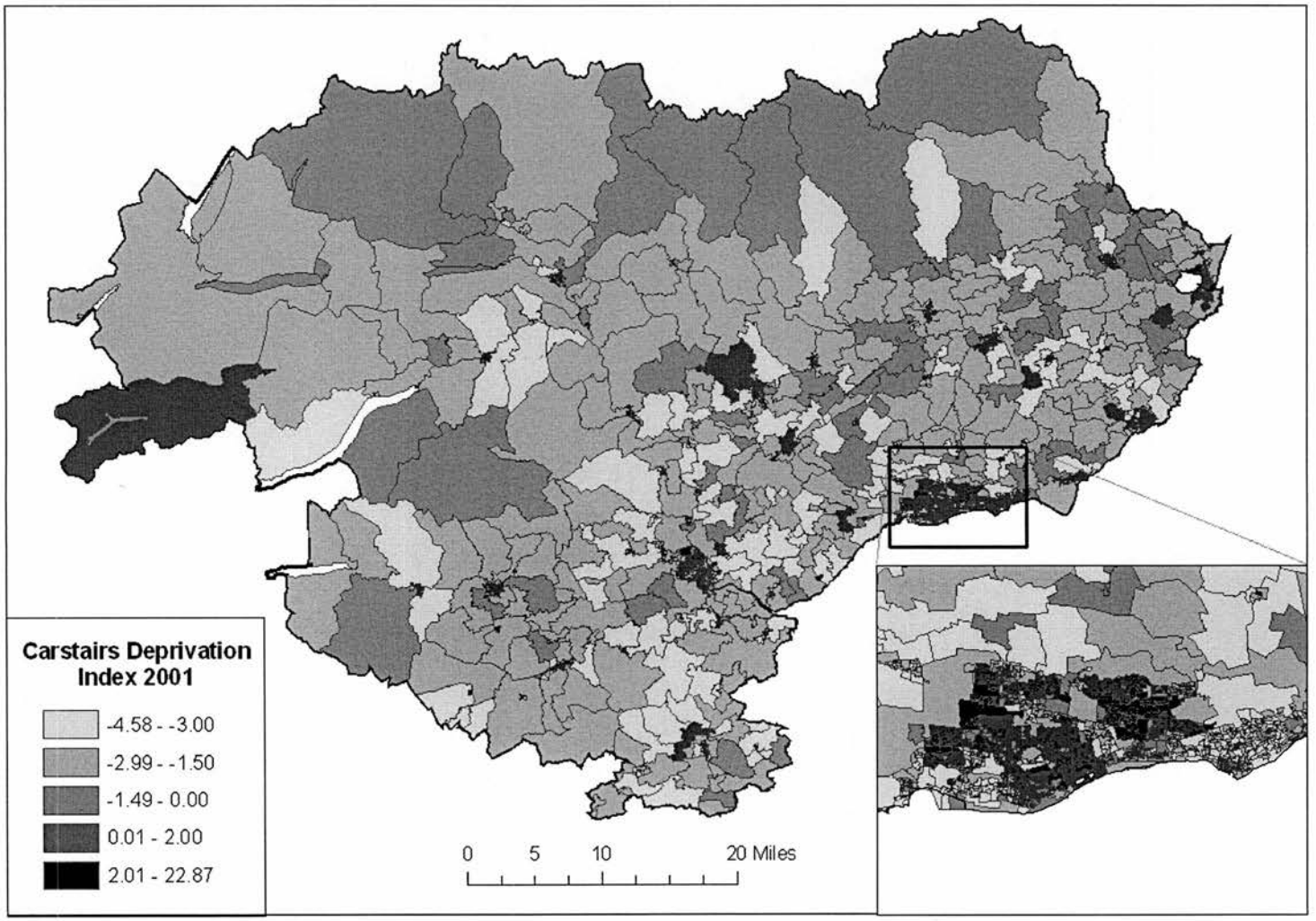


Figure 7.1 Carstairs deprivation by output areas in Tayside, Scotland, 2001

CHAPTER 8 – [MANUSCRIPT 3] CHILDHOOD TYPE 1 DIABETES, POPULATION MIXING AND THE HYGIENE HYPOTHESIS

Matthew Cox[1], Paul Boyle[1,2], Peter Davey[3], Zhiqiang Feng[1], Andrew D Morris[4]

1 School of Geography & Geosciences, University of St Andrews, St Andrews KY16 9AL

2 Social Dimensions of Health Institute, Universities of Dundee and St Andrews, Dundee DD6 4HJ

3 Clinical Pharmacology & Therapeutics (MEMO Unit), Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY

4 DARTS/MEMO Collaboration, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY

Submitted to *Social Science & Medicine*

8.1 Abstract

The hygiene hypothesis suggests that areas with lower levels of population mixing would have higher rates of childhood Type 1 diabetes because the children residing there had less exposure to infection in early life. Higher rates of childhood Type 1 diabetes have indeed been identified in areas with lower levels of population mixing, when measured as the diversity of origins of incomers to each small geographical area. However, this measure takes no account of the absolute size of in-migration to an area. We suggest that a new measure which combines both the absolute size of in-migration to an area and the diversity of origins of these in-migrants may be a better measure of population mixing and we calculate this, first, for all in-migrants and, second, for child in-migrants aged under 15. We hypothesise that places which attract few in-migrants from less diverse origins will have the highest rates of childhood Type 1 diabetes. We test this using data on childhood diabetes incidence for Tayside, Scotland, between 1998 and 2001 using denominator populations and population mixing measures derived from the 2001 Census. We show that this new population mixing measure, when calculated for child in-migrants aged under 15, is indeed more strongly associated with childhood Type 1 diabetes than a number of other measures of population mixing, including the diversity of origins of incomers. Our hypothesis is supported as places which attract few child in-migrants from less diverse origins have the highest rates of childhood Type 1 diabetes. We also consider a range of other socio-economic variables, none of which was significantly associated with childhood Type 1 diabetes.

Our results are consistent with the hygiene hypothesis, where reduced infection in early life reduces immunity to later infectious exposure, precipitating diabetes.

Abstract word count 289

Keywords Childhood Type 1 diabetes; population mixing; hygiene hypothesis; Tayside, Scotland; Poisson regression.

Article word count 5756 (including main text, abstract, endnotes, references and tables)

8.2 Introduction

Type 1 diabetes is a chronic disease that is on the rise in many parts of the developed world (Karvonen, Tuomilehto, Libman et al., 1993; Onkamo, Vaananen, Karvonen et al., 1999). The underlying aetiology of the disease is unclear and while there is a genetic component to Type 1 diabetes, environmental factors are also implicated (Drash, Lipton, Dorman, Becker, LaPorte, Orchard et al., 1991) and these may be multifactorial (Haverkos, 1997). Incidence peaks between the age of 5 and 15 and the autoantibodies which cause pancreatic islet cell destruction can appear years before onset, suggesting that potential environmental trigger(s) may operate in early life (Leslie & Elliott, 1994).

Certain viral infections such as Coxsackievirus B, rotavirus and the mumps virus have been implicated in the onset of Type 1 diabetes. However evidence from clinical and epidemiological studies for the role of specific viral agents is limited, suggesting that the link between diabetes and viral infection is time-dependent and complex. Depending on the 'autoimmune status' of the individual (determined by genes, age, and previous history of infection) and the nature of the virus, a viral infection may induce, protect against or indeed have no effect on the development of Type 1 diabetes (Bach, 2005; Filippi & von Herrath, 2005).

One theory regarding the protective effects of infection against Type 1 diabetes suggests that *reduced exposure* to common infections in early life may increase

susceptibility as early exposure to microbial antigens modifies the lymphocytic response to later immunological challenges. This 'hygiene hypothesis' has been supported by studies of rats and mice where the rates of diabetes are higher among those reared in a pathogen free environment (Leiter, Serreze, & Prochazka, 1990) and lower among those that have been exposed to viral infection or bacterial antigens in early life (Schwimmbeck, Dyrberg, & Oldstone, 1988; Wilberz, Partke, Dagnaes-Hansen et al., 1991).

A number of ecological studies have shown that the prevalence of Type 1 diabetes is higher in more rural areas with low population densities (Waugh, 1986), and less household overcrowding (Staines, Bodansky, McKinney et al., 1997). More recently, and building on work on childhood leukaemia (Stiller & Boyle, 1996), Type 1 diabetes has been shown to be negatively related to a 'population mixing' measure that summarises the diversity of origins from which child migrants into an area have come (Parslow, McKinney, Law et al., 2001). All of these studies use population mixing measures in the absence of reliable ecological information on infections (nor, indeed, is it known which infections should be considered, were such variables available). However at present there is no consensus as to the best way to measure population mixing. A number of variables have been used as proxies in the past, including the density of living, the presence of immigrants and the diversity of in-migrant origins.

In this study we test the hypothesis that childhood Type 1 diabetes will be negatively associated with population mixing within small areas of Tayside Health Board. To do this we use a number of variables which have been used previously (Bentham, 1994;

Parslow, McKinney, Law et al., 2001; Stiller & Boyle, 1996) to measure different dimensions of population mixing, namely, the population density of the local area, household overcrowding, the rate of immigration, the in-migration rate, and the diversity of origins from which in-migrants have moved. Low values of these variables would indicate low levels of population mixing and, according to the hygiene hypothesis, would be expected to have higher rates of childhood diabetes. Each of these variables could be argued to measure a different dimension of population mixing and may therefore be potentially valuable in helping to understand the aetiology of childhood diabetes. Thus, the household overcrowding and population density variables are useful surrogates for the spread of infection within the local area, but they would not provide information about the likely introduction of infections into the area. The rate of immigration may be more related to the introduction of new infection into an area, but immigration is a very rare event, especially in our study area. The measures which would appear to be more directly related to the introduction of new infections are the in-migration rate and the diversity of origins from which these incomers moved. The former provides an indication of the annual change in population within the local area attributable to migration. The latter provides an indication of the spread of places from which these migrants have originated.

While both the in-migration rate and the diversity of migrant origins measure different dimensions of population mixing, it is possible that different combinations of these two measures will have different implications for infection spread. We therefore calculated a new categorical population mixing variable which accounts for both the % of in-migrants and the diversity of origins of those in-migrants. A large number of in-

migrants from a narrow set of origins may not result in as much infection mixing as a large number of in-migrants from a diverse set of origins. Most importantly, we would expect areas with relatively low rates of child migration from less diverse origins to have the highest rates of diabetes.

We have also calculated each population mixing variable using data on both the total and the child population of each area, as it is possible that both may be important in explaining childhood disease. Susceptible children may be expected to come into daily contact with other children and we would expect these variables to be directly relevant to the spread of infection among this group. However, children may also have contact with adults perhaps directly, or through contacts made by their parents, so we have constructed these variables to examine whether they are related to childhood disease. We would expect *a priori* that they would not be as important as the child-based measures. Indeed, Parslow, McKinney, Law et al. (2001) found that the diversity of child in-migrants was more important than the diversity of total migrants in West Yorkshire.

8.3 Methods

We collected information from the DARTS database which has been described in detail elsewhere (Morris, Boyle, MacAlpine et al., 1997). In brief, routine data from the population of Tayside Health Board, Scotland, is record-linked using a unique patient identifier. Data sources include a register of all people with Type 1 and Type 2 diabetes

in Tayside, which has been validated and shown to have high sensitivity and specificity for the diagnosis of diabetes, a record of all inpatient hospital admissions in Tayside from 1980 with diagnostic codes from the International Classification of Diseases, version 9 (ICD9), and regional biochemistry and primary care records of all people with diabetes registered with the 78 general practices in Tayside that have all been inspected by dedicated research nurses. We studied 73 children (aged 0-14) diagnosed with Type 1 diabetes who were resident in Tayside in the years 1998-2001. Childhood Type 1 diabetes was defined as all children diagnosed with diabetes aged 0-14 who were insulin requiring within one month. Of the children studied, 34 were male and 39 were female. These cases were distributed across 85 census area statistics (CAS) sectors which are the geographical units used for the dissemination of the 2001 Census data in Scotland.

We modelled the 73 cases using Poisson regression. The number of males and females in each CAS sector was recorded separately, providing a maximum of 170 observations (85 x 2). In-migration data were not available for 3 small CAS sectors which were excluded from the study, resulting in 164 observations (82 x 2). There were no cases of childhood Type 1 diabetes during the study period in any of the excluded CAS sectors. The significance level for this analysis was set *a priori* at p=0.05.

The natural log of the 2001 child population, relevant to the sex of the particular observation, was included as an offset to control for the expected increase in the number of cases with the population size of the CAS sector. These populations were derived from the 2001 census data.

A series of demographic and socio-economic independent variables were modelled both alone and in combination and these included: the sex of the cases, the % of individuals in non-white ethnic groups; Carstairs deprivation; the % of unemployed economically active males; the % of households with no car; and the % of households in low social classes (IV or V according to the Registrar General's classification). We also included a set of population mixing variables as described below. The age and sex of the individual cases were known from the DARTS data, and the remaining variables were calculated ecologically from the 2001 Census.

Studies in the past have used different measures of population mixing to act as surrogates for infection spread, including population density, household overcrowding and migration mixing. Each of these variables represents a different aspect of population mixing and, at present, it is unknown which is the most important. Therefore we included a range of variables expected to influence the spread of infections across the CAS sectors. These were: household overcrowding (the % of people in households with 1 or more persons per room); population density (the number of residents in the CAS sector divided by the area measured in hectares); immigration (the % of people who have immigrated from abroad within the previous year); in-migration rate (the % of residents who had moved into the CAS sector from elsewhere in the UK in the previous year); and the diversity of the in-migrant origins (calculated using Shannon's entropy, Stiller & Boyle, 1996). Each of these variables was calculated for children and the total population separately (Table 8.1).

We also created two categorical variables by combining the percentage of in-migrants and the diversity of their origins. One variable considered child in-migrants and the other variable was calculated in the same way but included in-migrants of any age. Each variable consisted of four categories depending on whether the area had a child (total) in-migration rate that was above or below the mean child (total) in-migration rate for Tayside CAS sectors and, similarly, whether the diversity of origins for those child (total) in-migrants was also above or below average. Thus, each variable has four categories: the first category represents areas with high in-migration from a diverse set of origins; the second represents areas with high in-migration from a narrow set of origins; the third represents areas with low in-migration from a diverse set of origins; and the fourth represents areas with low in-migration from a narrow set of origins. Table 8.2 shows the number of areas in each category along side the distribution of childhood diabetes.

8.4 Results

Table 8.3 provides the results from a series of univariate Poisson regression models for children aged 0-14. Only one continuous population mixing variable was significantly related to childhood Type 1 diabetes at the 0.05 significance level: areas with a higher % of child residents who had migrated into the CAS sector in the previous year had significantly lower rates of diabetes ($p=0.013$). The entropy of total in-migrants which measures the diversity of incomers was marginally insignificant ($p=0.074$). Although no other measure of population mixing was significant, all were negatively related to

the incidence of childhood Type 1 diabetes as expected. The occurrence of Type 1 diabetes was not significantly different for males and females and was not significantly associated with the six socio-economic variables tested here. Multivariate models showed that no combination of variables improved the fit significantly.

We also compared the two categorical population mixing variables with Type 1 diabetes which compared the diversity and rate of child and total in-migrants (Table 8.3). The variable calculated from data on all migrants was not significant. However, the child-based variable was significant; areas with the highest incidence of diabetes were those with low child in-migration from a narrow set of origins ($p=0.002$). Indeed, as expected the incidence of diabetes in the base category (high in-migration from diverse origins) was significantly lower than the three remaining categories. Accordingly this model had the best fit of all the models, with a significantly lower log likelihood value than both child in-migration rate and the diversity of origins of child in-migrants variables when taken fitted separately.

8.5 Discussion

The hygiene hypothesis has been applied to the rising incidence of allergies (Kramer, Heinrich, Wjst, & Wichmann, 1999; Strachan, 1989), asthma (Ball, Castro-Rodriguez, Griffith, Holberg, Martinez, & Wright, 2000; Illi, von Mutius, Lau, Bergmann, Niggemann, Sommerfeld et al., 2001) and Type 1 diabetes (Parslow, McKinney, Law et al., 2001) among children. The results from this study provide further support for the hypothesised association between limited exposure to infections in early life and

childhood diabetes. In particular, we have shown that areas with low rates of child in-migration have higher rates of childhood Type 1 diabetes (Table 8.3). More importantly though, we found that areas with low child in-migration from a narrow set of origins had particularly high rates of diabetes (Table 8.3). One possible explanation is that these relationships reflect the importance of in-migration for bringing new infectives into areas. In tandem with the hygiene hypothesis, our results suggest that less exposure to infections in early life may result in an increased risk of childhood diabetes.

There are limitations with this study, the most obvious of which is the small sample size; it is possible that genuine relationships are not significant in this analysis because we do not have enough cases. It would be interesting to extend this analysis across Scotland and this extension is now being explored using the Study Group for the Care of Young Diabetics register (Rangasami, Greenwood, McSporran, Small, Patterson, & Waugh, 1997). There are also certain factors that are impossible to control for in this ecological study. Breastfeeding appears to be protective against Type 1 diabetes but figures on this are not available for small areas. However, deprivation is likely to be correlated with breastfeeding practices and this variable was not significant in our analysis (Table 8.3). Similarly, we could not identify whether our cases were delivered by Caesarean section, which has also been associated with increased risk of Type 1 diabetes (Dahlquist & Kallen, 1992; Patterson, Carson, Hadden, Waugh, & Cole, 1994). The distributions of diabetes was not explained either by the ethnic composition of the population or by population density, both factors previously associated with Type 1 diabetes in small geographical areas (McKinney, Law, Bodansky et al., 1996; Patterson, Carson, &

Hadden, 1996; Staines, Bodansky, McKinney et al., 1997). Note, though, that the ethnic minority group population in Tayside is small.

The results from previous studies provide conflicting evidence regarding the hygiene hypothesis (Anderson & Watson, 2001). Based on consultations with doctors Gibbon, Smith, Egger, Betts, & Phillips (1997) showed that reported infections (particularly respiratory infection) in the first year of life were associated with reduced risks of Type 1 diabetes among children. These results were in the same direction as those found by Blom, Dahlquist, Nystrom, Sandstrom, & Wall (1989) in Sweden (although the Swedish results were not significant). Pundziute-Lycka, Urbonaite, & Dahlquist (2000) found that infection in the first 6 months of life conferred protection against Type 1 diabetes after 5 years of age. McKinney, Okasha, Parslow, Law, Gurney, Williams et al., (2000) considered frequency of attendance at day-care during the first year of life, which is a good surrogate for exposure to infection, and showed that it was inversely related to childhood diabetes. An increasing number of children in day-care and the number of sessions that the children attended were also significantly associated with protection from diabetes. Similar results relating to day-care attendance were found in the EURODIAB study (2000). It has also been shown that risks are higher for the first-born and those children in smaller families (Bingley, Douek, Rogers, & Gale, 2000; Wadsworth, Shield, Hunt, & Baum, 1997).

Ecological studies have also shown that Type 1 diabetes is more prevalent among those who may be less exposed to infection in early life. Incidence has been related to climate (Dahlquist & Mustonen, 1994) and latitude (Dahlquist, Blom, Holmgren,

Hagglof, Larsson, Sterky et al., 1985). Rothwell, Staines, Smail, Wadsworth, & McKinney (1996) showed that there is a seasonal effect of month of birth related to childhood diabetes, which suggests that environmental risk factors may be seasonal in nature. Similar results were found in the Netherlands (Jongbloet, Groenewoud, Hirasing, & Van Buuren, 1998) but not in other European countries (Rothwell, Gutnikov, McKinney, Schober, Ionescu-Tirgoviste, & Neu, 1999), or in southwest England (Zhao, Demaine, & Millward, 2000).

More relevant to this study, incidence has been shown to be higher in rural Scotland than urban areas (Waugh, 1986), in places with low population densities and low levels of household overcrowding (Karvonen, Rusanen, Sundberg, Virtala, Colpaert, Naukkarinen et al., 1997; Patterson, Carson, & Hadden, 1996; Patterson, Smith, Webb, Heasman, & Mann, 1988; Staines, Bodansky, McKinney et al., 1997), and in less deprived areas of Scotland (Patterson & Waugh, 1992) and Northern Ireland (Patterson, Carson, & Hadden, 1996). A related study in Yorkshire examined the role of population mixing using a Shannon entropy measure, first used in a study of childhood leukaemia (Stiller & Boyle, 1996), which summarises the diversity of places from which in-migrants originate. This showed that areas that attracted child in-migrants from a less diverse set of origins had a significantly higher incidence of childhood diabetes for 0-14 years (Parslow, McKinney, Law et al., 2001).

Crow, Alberti, & Parkin (2000), on the other hand, found higher rates in poorer areas of north-east England. Also, studies of childhood Type 1 diabetes in both New South Wales (Verge, Silink, & Howard, 1994) and Poland (Grzywa & Sobel, 1995) did not

find significant urban/rural differences in incidence. Other studies in Turin (Bruno, Merletti, Vuolo, Pisu, Giorio, & Pagano, 1993) and the Polish city of Poznan (Rewers, LaPorte, Walczak, Dmochowski, & Bogaczynska, 1987) have identified significantly higher rates in urban areas than the surrounding rural areas. In Greece, Dacou-Voutetakis, Karavanaki, & Tsoka-Gennatas (1995) found higher rates in metropolitan and semi-rural areas than in rural or urban areas.

Methodological issues are also important, such as the scale of analysis. Most of the studies described above (other than Crow, Alberti, & Parkin 2000) used quite large areal units as the basis for their analyses. Our results for small geographical areas in the Tayside region of Scotland are in line with other studies conducted for small areas elsewhere in Britain (Parslow, McKinney, Law et al., 2001; Staines, Bodansky, McKinney et al., 1997). We also argue in this paper that it is unclear which measure of population mixing should be used. Like some studies, we did not find that Type 1 diabetes was associated with population density, but we did find a significant relationship with the percentage of child in-migrants – a variable which has rarely been considered previously, but which may be argued to be a reasonable measure of one aspect of population mixing within child populations. We also show that a more complex measure which is based on both the number and diversity of child in-migrants appears to be even more strongly associated with Type 1 diabetes.

The incidence of Type 1 diabetes has been rising in many north European countries during the last 30 years (Gibbon, Smith, Egger et al., 1997). It is possible that the hygiene hypothesis may account for this as a number of factors related to the reduced

exposure to infections for children seem to be at work. First, family sizes have been reducing, which means that children will come into contact with fewer infections at home (Gardner, Bingley, Sawtell, Weeks, & Gale, 1997). Second, the increasing hygienic awareness of parents and the increasing use of disposables and food industry products means that infections are kept at bay more easily (Kolb & Elliott, 1994). Third, counterurbanisation has dominated migration trends in many north European countries since the 1970s with people tending to move away from urban centres towards rural hinterlands (Boyle, 1995; Champion, 1994). These migrants are not usually taking up farming lifestyles, which may introduce infections through the frequent contact with various animals (Johnston & Openshaw, 2001), but are simply choosing to live in less densely populated areas with the consequence that their children may be exposed to fewer infections in early life.

The hygiene hypothesis suggests that contact with one or more pathogens in early life triggers an immunological response that confers protection against the onset of Type 1 diabetes among those with a genetic pre-disposition. Patterson, Carson, & Hadden (1996) suggest that the lack of space time clustering in childhood diabetes in Northern Ireland makes it less likely that a single infectious agent is responsible, although evidence for clustering has been found in Sweden (Samuelsson, Johansson, Carstensen, & Ludvigsson, 1994). Even were clustering significant, it does not necessarily mean that a single agent is responsible, as infection may simply increase peripheral insulin requirements in children who already have the disease (Dahlquist, 1993). More work is required to determine whether specific infections confer protection against Type 1 diabetes.

8.6 References

Anderson, W.J., & Watson, L. (2001). Conclusions about type 1 diabetes and hygiene hypothesis are premature. *Bmj*, 322(7299), 1429.

Bach, J.F. (2005). Infections and autoimmune diseases. *J Autoimmun*, 25 Suppl, 74-80.

Ball, T.M., Castro-Rodriguez, J.A., Griffith, K.A., Holberg, C.J., Martinez, F.D., & Wright, A.L. (2000). Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*, 343(8), 538-543.

Bentham, G. (1994). Population mixing and sudden infant death syndrome in England and Wales. *Int J Epidemiol*, 23(3), 540-544.

Bingley, P.J., Douek, I.F., Rogers, C.A., & Gale, E.A. (2000). Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group. *Bmj*, 321(7258), 420-424.

Blom, L., Dahlquist, G., Nystrom, L., Sandstrom, A., & Wall, S. (1989). The Swedish childhood diabetes study--social and perinatal determinants for diabetes in childhood. *Diabetologia*, 32(1), 7-13.

Boyle, P. (1995). Rural in-migration in England and Wales, 1980-1981. *J Rural Stud*, 11(1), 65-78.

Bruno, G., Merletti, F., Vuolo, A., Pisu, E., Giorio, M., & Pagano, G. (1993). Sex differences in incidence of IDDM in age-group 15-29 yr. Higher risk in males in Province of Turin, Italy. *Diabetes Care*, 16(1), 133-136.

Champion, A.G. (1994). Population change and migration in Britain since 1981: evidence for continuing deconcentration. *Environ Plan A*, 26(10), 1,501-520.

Cox, M. (2006). Haha. *junk mail*.

Crowley, T.J. (2000). Causes of Climate Change Over the Past 1000 Years. *Science*, 289(5477), 270-277.

Dacou-Voutetakis, C., Karavanaki, K., & Tsoka-Gennatas, H. (1995). National data on the epidemiology of IDDM in Greece. Cases diagnosed in 1992. Hellenic Epidemiology Study Group. *Diabetes Care*, 18(4), 552-554.

Dahlquist, G., Blom, L., Holmgren, G., Hagglof, B., Larsson, Y., Sterky, G., & Wall, S. (1985). The epidemiology of diabetes in Swedish children 0-14 years--a six-year prospective study. *Diabetologia*, 28(11), 802-808.

Dahlquist, G., & Kallen, B. (1992). Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes mellitus. *Diabetologia*, 35(7), 671-675.

Dahlquist, G. (1993). Etiological aspects of insulin-dependent diabetes mellitus: an epidemiological perspective. *Autoimmunity*, 15(1), 61-65.

Dahlquist, G., & Mustonen, L. (1994). Childhood onset diabetes--time trends and climatological factors. *Int J Epidemiol*, 23(6), 1234-1241.

Drash, A.L., Lipton, R.B., Dorman, J.S., Becker, D.J., LaPorte, R.E., Orchard, T.J., Riley, W.J., Trucco, M., & Kuller, L.H. (1991). The interface between epidemiology and molecular biology in the search for the causes of insulin-dependent diabetes mellitus. *Ann Med*, 23(4), 463-471.

EURODIAB (2000). Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. EURODIAB Substudy 2 Study Group. *Diabetologia*, 43(1), 47-53.

Filippi, C., & von Herrath, M. (2005). How viral infections affect the autoimmune process leading to type 1 diabetes. *Cell Immunol*, 233(2), 125-132.

Gardner, S.G., Bingley, P.J., Sawtell, P.A., Weeks, S., & Gale, E.A. (1997). Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. The Bart's-Oxford Study Group. *Bmj*, 315(7110), 713-717.

Gibbon, C., Smith, T., Egger, P., Betts, P., & Phillips, D. (1997). Early infection and subsequent insulin dependent diabetes. *Arch Dis Child*, 77(5), 384-385.

Grzywa, M.A., & Sobel, A.K. (1995). Incidence of IDDM in the province of Rzeszow, Poland, 0- to 29-year-old age-group, 1980-1992. *Diabetes Care*, 18(4), 542-544.

Haverkos, H.W. (1997). Could the aetiology of IDDM be multifactorial? *Diabetologia*, 40(10), 1235-1240.

Illi, S., von Mutius, E., Lau, S., Bergmann, R., Niggemann, B., Sommerfeld, C., & Wahn, U. (2001). Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *Bmj*, 322(7283), 390-395.

Johnston, S.L., & Openshaw, P.J. (2001). The protective effect of childhood infections. *Bmj*, 322(7283), 376-377.

Jongbloet, P.H., Groenewoud, H.M., Hirasing, R.A., & Van Buuren, S. (1998). Seasonality of birth in patients with childhood diabetes in The Netherlands. *Diabetes Care*, 21(1), 190-191.

Karvonen, M., Tuomilehto, J., Libman, I., & LaPorte, R. (1993). A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. World Health Organization DIAMOND Project Group. *Diabetologia*, 36(10), 883-892.

Karvonen, M., Rusanen, J., Sundberg, M., Virtala, E., Colpaert, A., Naukkarinen, A., & Tuomilehto, J. (1997). Regional differences in the incidence of insulin-dependent diabetes mellitus among children in Finland from 1987 to 1991. Childhood Diabetes in Finland (DiMe) Study Group. *Ann Med*, 29(4), 297-304.

Kolb, H., & Elliott, R.B. (1994). Increasing incidence of IDDM a consequence of improved hygiene? *Diabetologia*, 37(7), 729.

Kramer, U., Heinrich, J., Wjst, M., & Wichmann, H.E. (1999). Age of entry to day nursery and allergy in later childhood. *Lancet*, 353(9151), 450-454.

Leiter, E.H., Serreze, D.V., & Prochazka, M. (1990). The genetics and epidemiology of diabetes in NOD mice. *Immunol Today*, 11(5), 147-149.

Leslie, R.D., & Elliott, R.B. (1994). Early environmental events as a cause of IDDM. Evidence and implications. *Diabetes*, 43(7), 843-850.

McKinney, P.A., Law, G.R., Bodansky, H.J., Staines, A., & Williams, D.R. (1996). Geographical mapping of childhood diabetes in the northern English county of Yorkshire. *Diabet Med*, 13(8), 734-740.

McKinney, P.A., Okasha, M., Parslow, R.C., Law, G.R., Gurney, K.A., Williams, R., & Bodansky, H.J. (2000). Early social mixing and childhood Type 1 diabetes mellitus: a case-control study in Yorkshire, UK. *Diabet Med*, 17(3), 236-242.

Morris, A.D., Boyle, D.I.R., MacAlpine, R., Emslie-Smith, A., Jung, R.T., Newton, R.W., & MacDonald, T.M. (1997). The diabetes audit and research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. *British Medical Journal*, 315(7107), 524-528.

Onkamo, P., Vaananen, S., Karvonen, M., & Tuomilehto, J. (1999). Worldwide increase in incidence of Type I diabetes - The analysis of the data on published incidence trends. *Diabetologia*, 42(12), 1395-1403.

Parslow, R.C., McKinney, P.A., Law, G.R., & Bodansky, H.J. (2001). Population mixing and childhood diabetes. *Int J Epidemiol*, 30(3), 533-538; discussion 538-539.

Patterson, C.C., Smith, P.G., Webb, J., Heasman, M.A., & Mann, J.I. (1988). Geographical variation in the incidence of diabetes mellitus in Scottish children during the period 1977-1983. *Diabet Med*, 5(2), 160-165.

Patterson, C.C., & Waugh, N.R. (1992). Urban/rural and deprivational differences in incidence and clustering of childhood diabetes in Scotland. *Int J Epidemiol*, 21(1), 108-117.

Patterson, C.C., Carson, D.J., Hadden, D.R., Waugh, N.R., & Cole, S.K. (1994). A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. *Diabetes Care*, 17(5), 376-381.

Patterson, C.C., Carson, D.J., & Hadden, D.R. (1996). Epidemiology of childhood IDDM in Northern Ireland 1989-1994: low incidence in areas with highest population density and most household crowding. Northern Ireland Diabetes Study Group. *Diabetologia*, 39(9), 1063-1069.

Pundziute-Lycka, A., Urbonaite, B., & Dahlquist, G. (2000). Infections and risk of Type I (insulin-dependent) diabetes mellitus in Lithuanian children. *Diabetologia*, 43(10), 1229-1234.

Rewers, M., LaPorte, R.E., Walczak, M., Dmochowski, K., & Bogaczynska, E. (1987). Apparent epidemic of insulin-dependent diabetes mellitus in Midwestern Poland. *Diabetes*, 36(1), 106-113.

Rothwell, P.M., Staines, A., Smail, P., Wadsworth, E., & McKinney, P. (1996). Seasonality of birth of patients with childhood diabetes in Britain. *Bmj*, 312(7044), 1456-1457.

Rothwell, P.M., Gutnikov, S.A., McKinney, P.A., Schober, E., Ionescu-Tirgoviste, C., & Neu, A. (1999). Seasonality of birth in children with diabetes in Europe: multicentre cohort study. European Diabetes Study Group. *Bmj*, 319(7214), 887-888.

Samuelsson, U., Johansson, C., Carstensen, J., & Ludvigsson, J. (1994). Space-time clustering in insulin-dependent diabetes mellitus (IDDM) in south-east Sweden. *Int J Epidemiol*, 23(1), 138-142.

Schwimmbeck, P.L., Dyrberg, T., & Oldstone, M.B. (1988). Abrogation of diabetes in BB rats by acute virus infection. Association of viral-lymphocyte interactions. *J Immunol*, 140(10), 3394-3400.

Staines, A., Bodansky, H.J., McKinney, P.A., Alexander, F.E., McNally, R.J., Law, G.R., Lilley, H.E., Stephenson, C., & Cartwright, R.A. (1997). Small area variation in the incidence of childhood insulin-dependent diabetes mellitus in Yorkshire, UK: links with overcrowding and population density. *Int J Epidemiol*, 26(6), 1307-1313.

Stiller, C.A., & Boyle, P.J. (1996). Effect of population mixing and socioeconomic status in England and Wales, 1979-85, on lymphoblastic leukaemia in children. *Bmj*, 313(7068), 1297-1300.

Strachan, D.P. (1989). Hay fever, hygiene, and household size. *Bmj*, 299(6710), 1259-1260.

Verge, C.F., Silink, M., & Howard, N.J. (1994). The incidence of childhood IDDM in New South Wales, Australia. *Diabetes Care*, 17(7), 693-696.

Wadsworth, E.J., Shield, J.P., Hunt, L.P., & Baum, J.D. (1997). A case-control study of environmental factors associated with diabetes in the under 5s. *Diabet Med*, 14(5), 390-396.

Waugh, N.R. (1986). Insulin-dependent diabetes in a Scottish region: incidence and urban/rural differences. *J Epidemiol Community Health*, 40(3), 240-243.

Wilberz, S., Partke, H.J., Dagnaes-Hansen, F., & Herberg, L. (1991). Persistent MHV (mouse hepatitis virus) infection reduces the incidence of diabetes mellitus in non-obese diabetic mice. *Diabetologia*, 34(1), 2-5.

Zhao, H., Demaine, A.G., & Millward, B.A. (2000). Seasonality of birth in children with diabetes. Results of various studies differ. *Bmj*, 320(7236), 716.

8.7 Tables & figures

Variables	Minimum	Maximum	Mean	Standard Deviation
Type 1 Incidence:				
Male childhood Type 1 incidence	0	4	0.785	0.415
Female childhood Type 1 incidence	0	2	0.633	0.476
Socio-economic variables:				
% unemployment	1.740	15.780	5.690	3.497
% households no car	1.380	62.890	20.471	16.434
% low social class	3.880	21.940	13.467	4.408
% non-white	0.000	12.170	1.849	2.466
% children non-white	0.000	28.940	3.272	5.157
Carstairs deprivation	-4.680	6.010	-0.815	2.841
Total population mixing variables:				
Diversity of in-migrants	2.430	5.310	3.622	0.566
% in-migrants	4.540	36.620	9.718	5.982
% immigrants	0.000	8.540	0.723	1.411
% persons in overcrowded households	0.250	4.150	1.465	0.812
Population Density	0.007	80.040	12.466	19.286
Child population mixing variables:				
Diversity of child in-migrants	1.210	4.050	2.668	0.554
% child in-migrants	4.790	22.360	10.044	3.663
% child immigrants	0.000	9.160	0.628	1.344
% children in overcrowded households	0.000	39.580	13.62268	8.492
Population density of children	0.001	13.800	2.022	3.231

Table 8.1 Descriptive statistics for the continuous variables used in the analysis

Variables	Number of CAS Sectors	Total Cases
Combined total population mixing variable:		
1 - high in-migration & high diversity	24	4
2 - high in-migration & low diversity	16	2
3 - low in-migration & high diversity	58	28
4 - low in-migration & low diversity	66	39
Total	164	73
Combined child population mixing variable:		
1 - high child in-migration & high child diversity	30	4
2 - high child in-migration & low child diversity	30	6
3 - low child in-migration & high child diversity	64	40
4 - low child in-migration & low child diversity	40	23
Total	164	73

Table 8.2 Type 1 diabetes among children, 0-14, by combined measures of population mixing

Table 8.3 Type 1 diabetes among children, 0-14 (univariate models)

Variables	Parameter estimate	Standard error	p-value	Log likelihood
Socio-economic variables:				
Sex (female)	0.18557	0.234633	0.429	-124.36651
% low social class	0.00505	0.025273	0.842	-124.66014
% households no car	-0.01003	0.008465	0.236	-123.95120
% unemployment	-0.04066	0.033707	0.228	-123.90412
% non-white	-0.07375	0.074183	0.320	-124.11759
% children non-white	-0.04803	0.042162	0.255	-123.92270
Carstairs deprivation	-0.03372	0.038941	0.387	-124.29769
Individual total population mixing variables:				
Diversity of in-migrants	-0.42583	0.238517	0.074	-123.05956
% in-migrants	-0.06861	0.048417	0.156	-123.41984
% immigrants	-0.14079	0.241264	0.560	-124.47708
% persons in overcrowded households	-0.12310	0.142679	0.388	-124.29712
Population Density	-0.00004	0.000061	0.477	-124.41907
Combined total population mixing variable:				
1 - high in-migration & high diversity (base category)				-121.90918
2 - high in-migration & low diversity	0.87708	0.866025	0.311	
3 - low in-migration & high diversity	0.67830	0.534523	0.204	
4 - low in-migration & low total diversity	1.01647	0.525015	0.053	
Individual child population mixing variables:				
Diversity of child in-migrants	-0.34820	0.275895	0.207	-123.89622
% child in-migrants	-0.15586	0.062938	0.013*	-

				-121.08676
% child immigrants	-0.18923	0.226568	0.404	-124.24681
% children in overcrowded households	-0.01762	0.014771	0.233	-123.94203
Population density of children	-0.01895	0.0316859	0.550	-124.49659
Combined child population mixing variable:				
1 - high child in-migration & high child diversity (base category)				-117.62995
2 - high child in-migration & low child diversity	1.60172	0.645497	0.013*	
3 - low child in-migration & high child diversity	1.25265	0.524404	0.017*	
4 - low child in-migration & low child diversity	1.66819	0.541736	0.002*	

* Significant at $p<0.05$ level

CHAPTER 9 – [MANUSCRIPT 4] UPTAKE OF REAGENT STRIPS, DEPRIVATION AND ACCESS TO SERVICES

Matthew Cox[1], Josie Evans[2], Paul Boyle[1,3], Zhiqiang Feng[1], Peter Davey[4]

1 School of Geography & Geosciences, University of St Andrews, St Andrews, Scotland KY16 9AL

2 Epidemiology & Public Health, Community Health Sciences, University of Dundee

3 Social Dimensions of Health Institute, Universities of Dundee and St Andrews, Dundee, Scotland

4 Clinical Pharmacology & Therapeutics (MEMO Unit), Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY

Submitted to *Health & Place.*

9.1 Abstract

Type 2 diabetes is increasing in prevalence in developed societies. To prevent complications associated with diabetes, people with diabetes need to keep their blood glucose as close to normal levels as possible. One way to gauge how well controlled blood glucose levels are is to self-monitor using blood or urine glucose testing strips. We explore whether self-monitoring, measured through the uptake of dispensed testing strips, is influenced by geographical accessibility to pharmacies. Our results suggest that for patients with less advanced diabetes distance from pharmacies is indeed negatively associated with uptake. However, for insulin treated diabetes, distance has no effect.

Keywords

Type 2 diabetes; geographical access; self-monitoring; pharmacies; Tayside, Scotland.

9.2 Introduction

Type 2 diabetes is characterized by chronic increased levels of glucose in the blood (hyperglycaemia) and occurs in genetically susceptible people typically over the age of 40 years old (Diabetes UK, 2004). The condition is also strongly associated with lifestyle risk factors, including obesity and a lack of physical exercise (UK Prospective Diabetes Study Group, 1988), which are thought to lead to 'insulin resistance' whereby the cells of the body become desensitized to the action of insulin (the hormone controls the uptake of glucose by the cells for storage or as use for fuel). As insulin resistance increases the body will compensate by producing more insulin. However, if the body cannot produce enough insulin, periods of hyperglycaemia will result. Such hyperglycaemic episodes can directly damage the insulin producing β-cells of the pancreas and other sensitive cells (such as the retina of the eye, the kidneys or nerves) and eventually lead to their destruction. Any loss of β-cell function ('insulin deficiency') further undermines the person's ability to compensate for insulin resistance, increasing the likelihood of developing clinical diabetes, and most people with Type 2 diabetes display varying degrees of both insulin resistance and insulin deficiency (Bell & Hockaday, 1996). The prevalence of Type 2 diabetes is rising in the UK (Gatling, Budd, Walters, Mullee, Goddard & Hill, 1998; Harvey, Craney & Kelly, 2002) and throughout the developed world (Amos, McCarty & Zimmet, 1997; Passa, 2002; Wild, Roglic, Green, Sicree & King, 2004).

The treatment of Type 2 diabetes depends on the stage of the condition and the ability of the patient to control its effects and three broad approaches can be identified. In the early stages, patients can be treated quite simply by modifying their diet to include more complex carbohydrates, and which are low in glucose, saturated fat and salt. In association with increased physical exercise and weight loss this is often sufficient to counteract the effects of diabetes. However, patients whose Type 2 diabetes cannot be controlled by lifestyle changes alone are treated using a range of oral hypoglycaemic agents (tablets) which, depending on the exact agent, can inhibit the glucose processing mechanisms in the body, stimulate greater insulin production, or increase the efficacy of insulin on the cells of the body (ABPI, 2005). Finally, those who are unable to control their diabetes using the various tablet medication options are treated using injections of exogenous insulin. Hypertension and diabetes also frequently coexist (Gress, Nieto, Shahar, Wofford & Brancati, 2000), and therefore the blood pressure of a person with diabetes will be monitored at each medical consultation and anti-hypertensive medication may be prescribed if necessary.

All these treatments have essentially the same aim: to control and normalise blood glucose levels and blood pressure in order to negate the symptoms of hyperglycaemia and to avoid the long term complications of hyperglycaemia and hypertension. The altered metabolic state of diabetes results in micro- and macro- vascular damage, which manifest in an array of associated complications, including: retinopathy; nephropathy; neuropathy; cardiovascular disease; and peripheral vascular disease. Maintaining good control of both blood glucose and blood pressure of persons with Type 2 diabetes is of paramount importance for ensuring their future well-being. Good blood glucose

control has been observed to reduce both the risk of retinopathy and nephropathy by 33% (UK Prospective Diabetes Study Group, 1998b), and tight control of hypertension reduced the risk of heart disease by 56% and stroke by 44% in persons with Type 2 diabetes (UK Prospective Diabetes Study Group, 1998a, , 1998c, , 1998d).

Therefore successful blood glucose control is key to preventing complications of Type 2 diabetes and self-monitoring of blood glucose can play an important role in a person's ability to achieve this. Consequently, such monitoring is becoming increasingly common among people with Type 2 diabetes. A recent survey in the UK suggested that over 80% of people with Type 2 diabetes undertook some monitoring (Stewart, McCaig, Davie, Juroszek, Blackwood, Findlay et al., 2004), and the costs of monitoring in Type 2 diabetes are now higher than the cost of treatment with oral hypoglycaemic agents (Reynolds & Strachan, 2004).

There are two main forms of self-monitoring available in the UK: urine glucose and blood glucose monitoring. Urine testing is the simplest and involves placing a reagent strip in the urine stream, and checking changes in colour that indicate the presence of glucose in the urine. Although easy to conduct, the urine test has significant drawbacks as the relationship between urine and blood glucose levels is unreliable - a clear positive result will usually only be achieved with relatively high blood glucose concentrations. Also, urine strips can not detect hypoglycaemia (lowered blood glucose levels as a result of food intake, exercise, infection or medication). Urine analysis is therefore normally recommended for people with non-insulin dependent diabetes and for people who find blood testing difficult.

The alternative method is to test a sample of capillary blood taken by pricking the end of a finger with a lancet or needle. A spot of blood is then placed on a reagent strip, which may be designed to change colour (to be read manually or by a meter) or to be read by electrochemical means in a meter (ABPI, 2005). The results of blood glucose monitoring are far more accurate and reliable than those achieved by urine glucose monitoring and can also indicate low levels of blood sugar, providing warning of hypoglycaemia. For this reason, regular blood testing is recommended for all insulin treated patients and is encouraged for some non-insulin dependent patients who are struggling to control their diabetes. Both forms of self-monitoring should be performed on a daily basis but there is evidence that testing is often *ad hoc*, even by people with insulin dependent diabetes (Evans, Newton, Ruta et al., 1999).

Although it is generally accepted that self-monitoring of blood glucose is advisable for people with Type 1 diabetes (American Diabetes Association, 2001), the benefits of self-monitoring have not been clearly established in Type 2 diabetes (Gallichan, 1997). Several studies, including a meta-analysis, have failed to find an association between self-monitoring and improved glycaemic control in insulin-using patients with Type 2 diabetes (Coster, Gulliford, Seed, Powrie, & Swaminathan, 2000; Evans, Lawton, & Morris, 2004; Evans, Newton, Ruta et al., 1999; Harris, 2001). However, a recent study has found improvements in long-term outcomes among people who monitored, irrespective of treatment (Martin, Schneider, Heinemann, Lodwig, Kurth, Kolb et al., 2006).

The main components for self-monitoring are blood and urine glucose testing strips. To date, there has been no research on whether geographical access to pharmacies that dispense these strips influences their use. In this study we therefore consider whether the uptake of dispensed strips is related to the road distance to the nearest pharmaceutical units (dispensing community pharmacies and dispensing general practices). Uptake is therefore used as a proxy for whether or not a person with diabetes undertakes self-monitoring. We suspect that patterns of strip uptake will be different depending on the stage of the condition and we therefore conducted separate analyses by treatment type (diet treated, oral tablet treated and insulin treated). A person with diabetes treated by insulin is likely to perceive self-monitoring as more important than a person treated by diet changes or oral tablets. Also, clinicians may be more likely to present blood monitoring as mandatory to insulin treated patients while urine monitoring may be regarded as more voluntary for diet controlled patients.

This is the first study to consider the relationship between the uptake of glucose testing strips and geographical access to pharmacies, controlling for a range of demographic, socio-economic and clinical data that may also be related to strip uptake.

9.3 Data & Methods

The Diabetes Audit and Research in Tayside, Scotland (DARTS) population-based database (Morris, Boyle & MacAlpine, et al, 1997) is a comprehensive and reliable diabetes register, employing record linkage of multiple sources, and validation by a

team of dedicated nurses. From the DARTS dataset, 8,084 people with Type 2 diabetes were identified as residing in Tayside in 1999. For each case, information was available on their age and sex, the duration of their diabetes, and how their diabetes was treated. The dataset also contained clinical and pharmaceutical data for each case, including whether the subject had a previous medical complication associated with diabetes, whether they had attended a diabetes secondary care clinic, and whether they had been dispensed any blood glucose or urine glucose self-monitoring strips during 1999.

The type of self-monitoring carried out (and therefore the type of strips dispensed to the subject) was strongly related to the type of treatment the subject received. To take account of the different methods of self-monitoring undertaken by the different treatment groups, we focused upon the uptake of urine strips by persons with diet and tablet treated diabetes and blood strips for the persons with insulin treated diabetes. We treated uptake as a binary variable (0=no strips dispensed, 1=strips dispensed) and performed three multivariate logistic regression models. In Models 1 (diet treated diabetes) and 2 (tablet treated diabetes), we calculated the odds ratios of whether a person had cashed any prescription for urine glucose monitoring strips. In Model 3 (insulin dependent diabetes) we calculated the odds ratios for the uptake of prescriptions for blood glucose testing strips.

In this study we are particularly interested in the relationship between self-monitoring strip uptake and distance to the nearest pharmacy. In order to construct a measure of distance from each patient to their nearest pharmacy for our models we needed

geographical locations for the cases and for pharmacies in the area. The geographical location for each case was assigned to the population-weighted centroid of the output area (the smallest area for which data is available from the 2001 Census) they resided in. Of the 3,382 output areas in our Tayside study area, 2,786 were home to at least one person with Type 2 diabetes. The addresses for all pharmacies operating during 1999, in Scotland, were provided by ISD Scotland. By matching the postcode from the address to postcodes stored in the All Fields Postcode Directory data file, we were able to obtain geographic co-ordinates for each pharmacy. The two sets of coordinates were imported into a Geographical Information System (GIS) and linked to the Ordnance Survey Meridian road network. Using a 'network analyst' tool, we computed the road distance from the population weighted centroid of each output area to the nearest (in terms of distance) pharmacy along the Meridian road network.

We also included a number of variables expected to influence the uptake of self-monitoring strips: sex; age; duration of diabetes; deprivation; previous diabetic complications; secondary care clinic attendance; and uptake of blood testing strips (Model 1 and 2) or the uptake of urine testing strips (Model 3). Each of these variables was held at the individual-level on the DARTS database. In addition, as people from deprived areas have been shown in many studies to be less inclined towards health promoting behaviours (Ecob & Macintyre, 2000), and may therefore be less likely to self-monitor, we also used the output area of each case to calculate a Carstairs Deprivation Index score. The Carstairs score (Carstairs & Morris, 1989) is a commonly used deprivation score designed specifically for use in Scotland, which is calculated using four variables from the 2001 Census: % male unemployment; % car ownership;

% home ownership; and % low social class (belonging to social class IV and V according to the Registrar General's classification, i.e. working in semi-skilled and unskilled manual occupations). These variables are standardised and combined to form an overall score for each output area. However two output areas containing 19 of our subjects did not have Census data for male unemployment and were therefore omitted from the analysis (which was therefore conducted on the remaining 8,065 cases). The Carstairs Deprivation Index scores of the output areas of the cases in this study ranges from -4.58 to 9.62, and the mean score was -0.32. The Index is standardised so that a negative score indicates an output areas is less deprived than the Scottish average, and a positive score is more deprived.

9.4 Results

Table 9.1 shows the number of people with diabetes and the types of glucose monitoring strips dispensed to them in Tayside by treatment type in 1999. The largest group in the study were patients who were treated with oral hypoglycaemic agents (n=4,174), followed by diet treated patients (n=2,875) and insulin treated patients (n=1,303). The majority (75.9%) of people with diet treated diabetes did not cash any prescriptions for either blood or urine glucose testing strips, and therefore we assume did very little or no self-monitoring. Of the people with diet treated diabetes that were dispensed strips, nearly all were dispensed urine testing strips. Urine testing strips were also the dominant form of self-monitoring for persons with oral tablet treated Type 2 diabetes, although nearly half of these persons were not dispensed strips of any kind.

As we would expect, most of the persons with insulin treated diabetes (84.0%) were dispensed prescriptions for blood glucose testing strips.

The uptake of any urine strips during 1999 was significantly and negatively related to distance to the nearest pharmacy for both persons with diet and oral tablet treated diabetes (respectively: p=0.001; p=0.005), allowing for all other variables (Model 1 & 2, Table 9.2). This implies that people who live further away from pharmacies are less likely to be self-monitoring. Each kilometer away from the pharmacy was associated with a 9% decrease in the probability of having cashed a prescription for urine testing strips for persons with diet treated diabetes, and a 4% decrease for tablet treated diabetes.

Of the remaining variables, each year of age was associated with a 2% increase in the likelihood of any urine strip uptake for diet treated subjects (p<0.000), whereas each year of duration of diabetes was associated with a 2% decrease (p=0.013). Having had a diabetic complication before 1999 was associated with a 30% decrease (p=0.002). Attending a secondary care clinic was associated with the strongest effect on uptake, resulting in a 2.5 fold increase in the likelihood of cashing a prescription for urine testing strips for both persons with diet (p<0.000) and oral (p<0.000) treated diabetes. Persons with oral treated diabetes were also half as likely to have been dispensed urine strips if they had also been dispensed any blood testing strips during 1999 (p<0.000). Note that the number of people with diet treated diabetes using blood samples was extremely small (Table 9.1).

On the other hand, the likelihood of persons with insulin treated diabetes cashing a prescription for blood glucose testing strips was not significantly associated with distance to the closest pharmacy (Model 3, Table 9.2). Indeed only one variable, duration of diabetes, was significantly related to the uptake of any blood testing strips (p=0.09). Each additional year with diabetes was associated with 3% decrease in the likelihood of cashing a prescription for blood strips during the study period.

9.5 Discussion

This study has explored the uptake of self-monitoring strips among people with Type 2 diabetes. As expected, it demonstrates that monitoring is most common among persons with insulin-dependent diabetes and least likely among persons with diet-controlled diabetes. We would expect people who are insulin treated to be more likely to self-monitor and, in particular, to be more likely to undertake blood testing than those who are non-insulin treated. This was indeed borne out in the study: 72.0% of persons with insulin treated diabetes only cashed prescriptions for blood strips; and a further 11.7% cashing prescriptions for blood and urine strips. Conversely, large proportions of persons with non-insulin treated diabetes cashed no prescription at all for blood or urine testing strips (48.0% of oral treated; 75.9% of diet tablet treated).

The influence of geographical access to the dispensing pharmacy was also shown to be closely related to the type of treatment undertaken by the person with Type 2 diabetes. Controlling for other factors, we found that the uptake of urine strips was significantly

and negatively associated with the distance to the nearest pharmacy for both diet and tablet treated diabetes. However, the distance to the nearest pharmacy was not related to the uptake of blood testing strips for persons with insulin treated diabetes. One obvious interpretation is that due to the increased importance of self-monitoring for insulin treated patients they are less likely to allow distance-related inconvenience to prevent them from undertaking this important monitoring. The distance to the pharmacy may be more relevant when there is a voluntary aspect to monitoring, as may be the case for many persons with non-insulin treated diabetes, or when the patient perceives that their condition is not serious. The positive aspect of this result is that for those patients for whom glucose testing is most serious, geographical access to pharmacies is not a deterring factor. This suggests that while some of these patients still fail to test, this does not appear to be influenced by geography.

In Model 1 (diet treated diabetes), five variables were significantly related to the uptake of any urine strips: age, duration of diabetes, complications, secondary-care attendance, and distance to pharmacy. In Model 2 (tablet treated diabetes) three variables were related to any urine strip uptake: secondary-care attendance, any blood testing strips dispensed, and distance to pharmacy. However, Model 3 shows that the uptake of blood testing strips among persons with insulin dependent diabetes was not influenced significantly by any of the other clinical, demographic and deprivation variables we tested, except the duration of diabetes. This negative relationship (the longer a patient had the condition, the less likely they were to take up strips) may reflect a number of things. For instance, the patient may become increasingly disenchanted with the pain

and inconvenience of blood glucose monitoring over time. Alternatively, the greater experience of patients may mean that they have more control of their condition and therefore have less need to test their glucose levels. However, overall, the fact that so few variables influenced this group's uptake suggests that there is no obvious factor that could be targeted to help improve adherence rates.

A previous study by Evans, Newton, Ruta, MacDonald, Stevenson, & Morris (1999) of strip uptake in Tayside showed that 20% of people with insulin dependent Type 2 diabetes were not dispensed any blood testing strips in 1993-5. Our analysis shows that the proportion of people with insulin dependent Type 2 diabetes undertaking blood glucose monitoring has increased, as this figure has fallen to 13.2% during the 1999 study period. Evans, Newton, Ruta et al. also observed that the mean number of strips dispensed fell with increasing age and with deprivation for persons with insulin dependent Type 2 diabetes. This study is not directly comparable as it is focuses on the uptake of any strips rather the number of strips dispensed to each individual. However, in our study, age was only significant when modelling the uptake of any urine strips by persons with diet treated diabetes. Similarly Carstairs Deprivation Index was marginally insignificant for diet treated diabetes ($p=0.073$) and insignificant for the other treatment groups.

One of the novel features of this study is the use of GIS software to calculate the distance to the nearest pharmacy. GIS has become an increasingly popular tool to measure the impact of geographical access on health care delivery (McLafferty, 2003; Phillips, Kinman, Schnitzer, Lindbloom, & Ewigman, 2000), but the application of

GIS-based techniques to pharmaceutical dispensing is new. The methods we have used to measure access are similar to those used in employed in other studies (see Higgs, 2004 for a review). For instance, Higgs & White (2000) employed population-weighted centroids to locate demand points in rural areas for services, and a number of studies have calculated travel distances and travel times along road networks to the nearest health care facilities (Parker & Campbell, 1998; Perry & Gesler, 2000; Rosero-Bixby, 2004). However, we should bear in mind that the use of the nearest facility in this and other studies could be problematic, as the person may prefer to travel further in return for benefits offered from the greater choice of facilities (Haynes, Lovett, & Sunnenberg, 2003). In the context of pharmacies, such benefits may include: a family or personal connection to a particular service; convenient opening hours; a better range of services; fewer stock shortages; better parking facilities or transport linkages; or the pharmacy may fit better into the daily routine. In particularly, some patients may prefer to visit a pharmacy close to their place of work, although it should be noted that the average age of the persons in this study was over state retirement age (66.0 ± 12.1 s.d. years old) and some of those not of retirement age may have given up work due to their ill health. Unfortunately, at the time of this study, there was no information available regarding the actual pharmacies used by each subject to cash their prescription.

Despite these limitations, the significant negative relationship between uptake of urine strips and distance to pharmacy suggests that access is an important determinant of self-monitoring for persons with non-insulin treated diabetes. At present, there is some controversy as to whether self-monitoring improves glycaemic control in these non-insulin treated groups. In this study, 2,208 of the people with non-insulin treated

diabetes (32.7%) cashed prescriptions for urine testing strips, which may or may not improve glycaemic control. However, it should also be noted that persons with Type 2 diabetes may choose to urine monitor for other reasons, such as for peace of mind, or their comparative ease of use. In this case, people with Type 2 diabetes who live further away from pharmacies are disadvantaged in comparison to those that live relatively nearby.

This access issue is policy-relevant, as the provision of pharmacy services in Scotland is continually under debate. Currently, the Scottish Executive is committed to maintaining access to pharmaceutical services in rural areas via its 'Strategy for Pharmaceutical Care' (Scottish Executive, 2001) and the Executive operates an 'Essential Small Pharmacy Scheme' to help fund rural pharmacies. However, there remains concern that the possible deregulation of pharmaceutical healthcare services in the future could lead to the closure of small rural services (Rural Development Comittee, 2003). Our results suggest that such closures could reduce self-monitoring among Type 2 diabetes.

9.6 Acknowledgements

The authors wish to thank Julia Lawton and Diabetes UK (small grant ref: RD03/0002637) for their contribution to the original research project from which the uptake data used in this paper was drawn.

9.7 References

ABPI (2005). *Target Diabetes*: Association of the British Pharmaceutical Industry

American Diabetes Association (2001). Standards of medical care for people with diabetes mellitus (Position Statement). *Diabetes Care*, Suppl 1, S33-S41.

Bell, J.I., & Hockaday, T.D.R. (1996). Diabetes Mellitus. In D.J. Weatherall,J.G.G. Ledingham, & D.A. Warrell (Eds.), *Oxford Textbook of Medicine* (pp. 1448-1504).

Coster, S., Gulliford, M.C., Seed, P.T., Powrie, J.K., & Swaminathan, R. (2000). Self-monitoring in Type 2 diabetes mellitus: a meta-analysis. *Diabetic Medicine*, 17(11), 755-761.

Diabetes UK (2004). Diabetes in the UK: A Report from Diabetes UK.

Ecob, R., & Macintyre, S. (2000). Small area variations in health related behaviours; do these depend on the behaviour itself, its measurement, or on personal characteristics? *Health & Place*, 6(4), 261-274.

Evans, J.M.M., Newton, R.W., Ruta, D.A., MacDonald, T.M., Stevenson, R.J., & Morris, A.D. (1999). Frequency of blood glucose monitoring in relation to glycaemic control: Observational study with diabetes database. *British Medical Journal*, 318(7202), 83-86.

Evans, J.M.M., Lawton, J.M., & Morris, A.D. (2004). Final report for research grant RD03/0002637. Living by numbers: Self-monitoring patterns among people with type 2 diabetes. . *Unpublished.*

Gallichan, M. (1997). Self monitoring of glucose by people with diabetes: Evidence based practice. *British Medical Journal*, 314(7085), 964-967.

Harris, M.I. (2001). Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care*, 24(6), 979-982.

Haynes, R., Lovett, A., & Sunnenberg, G. (2003). Potential accessibility, travel time, and consumer choice: geographical variations in general medical practice registrations in Eastern England. *Environment and Planning A*, 35(10), 1733-1750.

Higgs, G., & White, S. (2000). Alternatives to census-based indicators of social disadvantage in rural communities. *Progress in Planning*, 53, 1-81.

Higgs, G. (2004). A Literature Review of the Use of GIS-Based Measures of Access to Health Care Services. *Health Services & Outcomes Research Methodology*, 5, 125-145.

Martin, S., Schneider, B., Heinemann, L., Lodwig, V., Kurth, H.J., Kolb, H., Scherbaum, W., & ROSSO Study Grp (2006). Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. *Diabetologia*, 49(2), 271-278.

McLafferty, S.L. (2003). GIS and health care. *Annual Review of Public Health*, 24, 25-42.

Parker, E.B., & Campbell, J.L. (1998). Measuring access to primary medical care: some examples of the use of geographical information systems. *Health & Place*, 4(2), 183-193.

Perry, B., & Gesler, W. (2000). Physical access to primary health care in Andean Bolivia. *Social Science & Medicine*, 50(9), 1177-1188.

Phillips, R.L., Kinman, E.L., Schnitzer, P.G., Lindbloom, E.J., & Ewigman, B. (2000). Using geographic information systems to understand health care access. *Archives of Family Medicine*, 9(10), 971-978.

Reynolds, R.M., & Strachan, M.W. (2004). Home blood glucose monitoring in type 2 diabetes. *British Medical Journal*, 329(7469), 754-755.

Rosero-Bixby, L. (2004). Spatial access to health care in Costa Rica and its equity: a GIS-based study. *Social Science & Medicine*, 58(7), 1271-1284.

Rural Development Comittee (2003). *Inquiry into Integrated Rural Development. Volume 2: Evidence.* http://www.scottish.parliament.uk/business/committees/historic/x-rural/reports-03/rar03-01-vol02-05.htm

Scottish Executive (2001). Right Medicine: A Strategy for Pharmaceutical Care in Scotland.

Stewart, D., McCaig, D., Davie, A., Juroszek, L., Blackwood, L., Findlay, N., & McCarthy, S. (2004). Glucose self-monitoring in primary care: a survey of current practice. *Journal of Clinical Pharmacy and Therapeutics*, 29(3), 273-277.

UK Prospective Diabetes Study Group (1988). UK Prospective Diabetes Study. IV. Characteristics of newly presenting type 2 diabetic patients: male preponderance and obesity at different ages. Multi-center Study. *Diabet Med*, 5(2), 154-159.

UK Prospective Diabetes Study Group (1998a). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, 352(9131), 837-853.

UK Prospective Diabetes Study Group (1998b). Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *Bmj*, 317(7160), 713-720.

UK Prospective Diabetes Study Group (1998c). Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *Bmj*, 317(7160), 703-713.

UK Prospective Diabetes Study Group (1998d). Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. *Bmj*, 317(7160), 720-726.

9.8 Tables

		Diet treated		Oral treated		Insulin treated	
		n	%	n	%	n	%
Type of strips dispensed during 1999	Blood & urine strips	18	0.7	195	4.7	153	11.7
	Blood strips only	70	2.7	516	12.4	942	72.3
	Urine strips only	536	20.7	1,459	34.9	36	2.8
	Neither blood or urine strips	1,963	75.9	2,005	48.0	172	13.2
	Total	2587	100.0	4175	100.0	1303	100.0

Table 9.1 Number of persons with Type 2 diabetes by treatment and the type of glucose testing strips dispensed, Tayside, 1999.

	Model 1 Diet treated, Urine strip uptake			Model 2 Oral treated, Urine strip uptake			Model 3 Insulin treated, Blood strip uptake		
Variable	Odds ratio	95% CIs	p-value	Odds Ratio	95% CIs	p-value	Odds Ratio	95% CIs	p-value
sex (female)	0.90	0.74 - 1.10	0.303	1.00	0.88 - 1.14	0.948	1.17	0.87 - 1.59	0.295
age (years)	1.02	1.02 - 1.03	0.000	1.00	1.00 - 1.01	0.113	1.01	0.99 - 1.02	0.215
duration of diabetes (years)	0.98	0.96 - 1.00	0.013	1.01	0.99 - 1.02	0.357	0.97	0.96 - 0.99	0.009
carstairs deprivation	1.04	1.00 - 1.08	0.073	1.00	0.97 - 1.03	0.992	0.97	0.91 - 1.02	0.248
complication pre-1999	0.70	0.55 - 0.88	0.002	0.90	0.78 - 1.04	0.153	1.07	0.77 - 1.49	0.682
secondary care clinic attendance	2.57	1.74 - 3.79	0.000	2.47	1.73 - 3.54	0.000	2.22	0.75 - 6.53	0.149
any blood strips dispensed	1.07	0.62 - 1.83	0.810	0.53	0.44 - 0.63	0.000	-	- - -	-
any urine strips dispensed	-	- - -	-	-	- - -	-	0.78	0.52 - 1.17	0.235
distance to pharmacy (kms)	0.91	0.87 - 0.96	0.001	0.96	0.93 - 0.99	0.005	1.02	0.95 - 1.10	0.600

Table 9.2 Multiple logistic regression models for the uptake of urine testing strips for persons with diet and oral tablet treated diabetes or blood testing strips for person with insulin treated diabetes

CHAPTER 10 – DISCUSSION & CONCLUSIONS

10.1 Discussion of results

Diabetes is the condition of chronic hyperglycaemia resulting from an unknown number of disease processes. It can be split into two broad aetiological categories: Type 1 diabetes (involving autoimmune disease processes) and Type 2 (involving non-autoimmune disease processes). As Type 1 and Type 2 diabetes have different pathogenic factors it is not too surprising to find that their geographic distributions are also different. For instance, Type 2 diabetes incidence is most common in socio-economically deprived settings, and this has been shown here for Tayside (Figure 4.10).

Most previous studies that relate Type 2 diabetes to deprivation have used prevalence data, based on a person's residential location at the time of study, rather than incidence data, which is based on a person's location at time of diagnosis (e.g. Benach, Yasui, Borrell et al., 2001; Connolly, Unwin, Sherriff et al., 2000; Evans, Newton, Ruta et al., 2000). However, it is possible that health-selective migration following diagnosis may alter the diabetes/deprivation relationship, perhaps widening the gap between the most and least deprived areas. In fact, a comparison of the deprivation circumstances for a cohort of Type 2 diabetics at: a) time of diagnosis and b) 8-18 years later, shows that, following diagnosis, people with Type 2 diabetes tend to be less likely to leave the most deprived areas than the general population. Thus, health-selective immobility, rather

than mobility, appears to be the selection effect that causes the relationship between diabetes and deprivation to widen over time (Table 6.3). Therefore, prevalence studies which imply a link with area deprivation should be viewed with some caution: though these studies are most likely correct in their assertion that the development of diabetes is linked to deprivation, the strength of this relationship may be over- or under-estimated due to health-selective migration. This study shows the importance of using diabetes incidence rather than prevalence, and thus incidence data was used in the remainder of the thesis.

The second broad question examined in this thesis considered the role of relative deprivation on the incidence of diabetes in small geographical areas. As a consequence, this thesis provides the first study which shows that the deprivation of an area *and* the deprivation circumstances of the surrounding areas both have a significant effect on diabetes incidence (Table 7.2). Thus, after allowing for deprivation within the output area, areas surrounded by relatively less deprived areas had lower incidence of Type 2 diabetes than expected, and output areas surrounded by more deprived areas had higher incidence. Previous debates have centred on whether the relationship between area-based deprivation and adverse health outcomes were contextual or compositional in nature (Fiscella & Franks, 2000; Sloggett & Joshi, 1994; Yen & Kaplan, 1999). However, the deprivation inequality measure used in this study is purely contextual, identifying socio-spatial effects on the incidence of diabetes. The development of diabetes is not only related to one's personal characteristics, but is also influenced by the characteristics of the area and people that surround them in their daily lives. The negative direction of the relationship shown in Chapter 7 (i.e. less deprived areas

surrounded by more deprived areas have higher rates of Type 2 diabetes, and *vice versa*) suggests a 'pull-up/push-down' mechanism (Gatrell, 1997), i.e. those who can benefit from collective social and material resources nearby but outside their own area of residence are less likely to develop Type 2 diabetes. These results do not support a local 'relative inequality hypothesis', where we would expect the psycho-social effects of being surrounded by more affluent people to have a negative effect on health outcomes, and this is consistent with the results of a number of other studies (reviewed in Stafford & Marmot, 2003).

From a visual inspection of mapped incidence rates (Figure 4.8), it is difficult to appraise the geography of Type 1 diabetes within small areas of Tayside due to the small number of cases. However, it appears that, unlike Type 2 diabetes incidence, Type 1 incidence is not associated with socio-economic deprivation in Tayside (see section 8.4 and Table 8.3). Interestingly, some previous studies have shown that population mixing appears to be negatively associated with the development of childhood diabetes (Parslow, McKinney, Law et al., 2001), and this is supported here for Tayside. The percentage of child in-migrants was negatively related to childhood Type 1 diabetes incidence ($p=0.013$). Similarly areas with the highest incidence of childhood Type 1 diabetes were those with a low percentage of child in-migrants from a narrow set of origins ($p=0.002$).

In the context of the 'hygiene hypothesis' (which assumes that contact with infections in early life can help children build up protective immunity which reduces the risk of certain allergic disorders), the results suggest that the in-migration of children may

introduce new pathogens into an area, which circulate in the childhood population and provide a protective effect against the development of Type 1 diabetes. Though this appears to be a fair assumption, this explanation should be treated with some caution since there is currently no evidence that population mixing measures are actually related to the introduction of new pathogens or to the circulation of pathogens between children. However, at present population mixing measures are the best proxies available for the potential exposure to pathogens.

Although the majority of this thesis has explored the distribution of incident cases of diabetes, there are other important geographies relating to diabetes. Self-monitoring is a vital component of blood glucose management and can have a positive impact on the lives of people with diabetes. For instance, it can provide peace of mind and educate patients about the best way to maintain control blood glucose concentrations (WHO, 1999). In turn, careful blood glucose management can help avoid diabetic complications. The process of testing blood glucose is relatively simple, but it involves patients cashing prescriptions for different types of testing strips at pharmacies. There have been many studies of the impact of travel times/distance on utilisation of healthcare services (see Higgs, 2004) and this thesis demonstrates that the uptake of testing strips is indeed affected by where the person with Type 2 diabetes lives. People with Type 2 diabetes in Tayside who are treated with diet interventions or oral hyperglycaemic agents, are less likely to cash a prescription for urine testing strips the further away from the nearest pharmacy they live (see section 9.4 and Table 9.2). On the other hand, people with more advanced diabetes, and are treated with insulin, are

not put off cashing prescriptions for blood testing strips by the distance to the pharmacy.

Other factors were controlled for in this analysis, showing that the patient's age, the duration of diabetes, previous diabetes-related complications and attendance at a secondary care clinic were related to strip uptake in some of the three treatment groups. However, while the uptake of both blood and urine testing strips was not significantly related to deprivation, the distance a patient lived from a pharmacy was, at least for those using urine strip monitoring.

10.2 Limitations of the study

The DARTS dataset (see section 4.3) provided all the diabetes-related data analysed in this thesis, and therefore the advantages and limitations of DARTS were also conferred upon this study. A major advantage of this study was the ability to consider the *incidence* of Type 2 diabetes and this is quite unique in a UK context. However, DARTS has a number of limitations that have at times impacted on the breadth, or the precision, possible in this study. For instance:

1. *Only aggregated DARTS data could be used, despite the DARTS dataset consisting of individual patient records.* The variety and accuracy of the spatial analytical techniques used in this thesis could have been improved if the location of each person with diabetes was provided at the postcode unit level (i.e. full postcode). Due to confidentiality constraints, this was not possible.

2. *DARTS data only goes back to the point at which the person was diagnosed.* We cannot assess the influence of earlier life environments on the development of diabetes. This is more of a problem with regard to Type 2 diabetes, as the onset of the Type 1 diabetes typically occurs at a much younger age, and therefore there is a shorter period of time in which the person could have migrated or the circumstances of the area they live in to have changed. However, the various risk factors for Type 2 diabetes are likely to act throughout the lifecourse (see Figure 2.1). Although this study shows that using area of residence at the time of diagnosis is preferable to using prevalence data, it is still possible that the development of diabetes was triggered by exposure to environmental factors whilst resident in a different area prior to diagnosis. For instance, the development of Type 2 diabetes may be related to the socio-economic deprivation experienced in early life and childhood and the relationship between deprivation and diabetes incidence is likely to reflect environmental conditions both in the place of residence at diagnosis and places of residence earlier in life. If this is true, then one might expect that people who have lived in deprived areas all their life would have a greater probability of developing Type 2 diabetes than people who have only lived in deprived areas in early life or later life. Unfortunately, addressing this interesting research question was outwith the capabilities of this study, as DARTS only records people once they have been diagnosed with diabetes and does not include any retrospective information on these people.

3. *At the time of analysis, DARTS data was only available for 1998-2001.* Due to the relatively low incidence rate of Type 1 diabetes, there were only 220 people diagnosed during this time period, and only 73 of this number were children. This made assessing the geographic distribution of Type 1 diabetes difficult. The study of childhood Type 1 diabetes and population mixing used Poisson regression techniques often used for small count data, such as for rare diseases. Even so, these analyses could be improved as more years of data become available.

4. *Uptake of testing strips does not mean they were used.* Though the prescribing data linked into the DARTS system provides information on whether a person has been dispensed any monitoring strips, it is not possible to know if those strips were used. Obviously, it would seem surprising if many patients were making the effort to pick up strips and then not using them, particularly as there is no formal medical system for checking whether they cashed prescriptions, but it is possible that this could happen in some cases.

There were other limitations with the analyses presented here which were not associated with DARTS. For instance, the testing of 'relative inequality hypothesis' at the local area level (Chapter 7) would have been more comparable with other work in the field if it had been possible to use 'income inequality' rather than 'deprivation inequality'. This was not possible since there is no income question on the UK Census of Population.

For the study of childhood Type 1 diabetes (Chapter 8), it would have been advantageous to allow for other suspected environmental risk factors, such as the early cessation of breast feeding, and the consumption of cow's milk and foods high in N-nitroso compounds (see section 2.2.4.3b), though no routine dataset is available with this information.

Finally, there were a number of limitations associated with the measure of geographic access to pharmacies with regard to glucose testing strip uptake (Chapter 9). Firstly, at the time, it was not possible to pinpoint which pharmacy had actually been used to cash prescriptions and therefore the study was restricted to using the nearest pharmacy to the patient's residential address. In truth, people may choose to use other pharmacies if they have easier access, better services, or if they are more convenient within their daily routines. Secondly, the measure of access used was the road distance between the population-weighted centroid of the output area and the postcode-based centroid of the nearest pharmacy. This assumes that every person cashing their prescription has travelled by car. However people may walk or rely on public transport, and therefore, although they are likely to travel similar distances to the pharmacy, the time spent travelling to the pharmacy will vary between different groups of patients.

10.3 Conclusions

There is considerable heterogeneity of the incidence of diabetes in small areas of Tayside. The geographic distribution of diabetes is dependent on the Type of diabetes and the demographic group observed. The incidence of Type 2 diabetes is higher in small areas which experience socio-economic deprivation and that are surrounded by other deprived areas – suggesting that areas of concentrated deprivation are more prone to Type 2 diabetes. People also tend to live in more deprived areas following diagnosis with Type 2 diabetes. Conversely, there is no relationship between Type 1 diabetes incidence and deprivation. Instead, childhood Type 1 diabetes incidence is higher in areas where there are few child in-migrants from a narrow set of origins – offering some support for the hygiene hypothesis of Type 1 diabetes causation. Finally, the distance to pharmacies impacts on whether a person with Type 2 diabetes carries out any glucose self-monitoring, but only for those who control their diabetes via diet interventions or oral hyperglycaemic agents: people treating Type 2 diabetes with insulin, and for whom self-monitoring is most important, are not significantly deterred.

10.4 Future Work

Future work arising from this thesis could include:

1. *A longitudinal study of Type 2 diabetes.* Information relating to the risk of developing diabetes could be gleaned by identifying participants of

longitudinal studies with Type 2 diabetes, depending on the exact longitudinal dataset available. Additionally, the benefit of a longitudinal study is that it is likely to include past residential history and this could be used to explore how socio-economic status at various stages through the life course affects the probability of developing Type 2 diabetes.

2. *A study of population mixing and childhood Type 1 diabetes using a national dataset.* The major problem encountered whilst investigating geographic variations in the incidence of childhood Type 1 diabetes in this thesis was the small number of cases diagnosed within Tayside during the study period. A study conducted using national data would have a greater number of cases and therefore greater statistical power. To this effect, the author and other members of the School of Geography & Geosciences are replicating the population-mixing study using childhood Type 1 incidence data for the whole of Scotland recently released to us by the Scottish Study Group for the Care of Diabetes in the Young.

3. *A study of the relationship between Type 1 diabetes and nitrate in drinking water.* Nitrate is a suspected environmental risk factor for Type 1 diabetes (Parslow, McKinney, Law et al., 1997). Methods similar to those used in this thesis could investigate the influence of nitrate using all Type 1 diabetics within the Tayside Health Board, or on a larger scale, for Scotland using the childhood Type 1 diabetes data from the Scottish Study Group for the Care of Diabetes in the Young (see previous point). The success of such a study

would be dependent on available information regarding past measurement of nitrate in the water supply from water companies or environmental agencies.

REFERENCE LIST

ABPI (2005). *Target Diabetes*: Association of the British Pharmaceutical Industry

Agardh, E.E., Ahlbom, A., Andersson, T., Efendic, S., Grill, V., Hallqvist, J., & Ostenson, C.G. (2004). Explanations of socioeconomic differences in excess risk of type 2 diabetes in Swedish men and women. *Diabetes Care*, 27(3), 716-721.

Åkerblom, H.K., & Knip, M. (1998). Putative environmental factors in Type 1 diabetes. *Diabetes/Metabolism Reviews*, 14(1), 31-67.

Åkerblom, H.K., Vaarala, O., Hyoty, H., Ilonen, J., & Knip, M. (2002). Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet*, 115(1), 18-29.

American Diabetes Association (2001). Standards of medical care for people with diabetes mellitus (Position Statement). *Diabetes Care*, Suppl 1, S33-S41.

Amos, A.F., McCarty, D.J., & Zimmet, P. (1997). The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. *Diabetic Medicine*, 14(12), S7-S85.

Anderson, J.T., Cornelius, J.G., Jarpe, A.J., Winter, W.E., & Peck, A.B. (1993). Insulin-dependent diabetes in the NOD mouse model. II. Beta cell destruction in autoimmune diabetes is a TH2 and not a TH1 mediated event. *Autoimmunity*, 15(2), 113-122.

Anderson, W.J., & Watson, L. (2001). Conclusions about type 1 diabetes and hygiene hypothesis are premature. *Bmj*, 322(7299), 1429.

Armstrong, J., Dorosty, A.R., Reilly, J.J., & Emmett, P.M. (2003). Coexistence of social inequalities in undernutrition and obesity in preschool children: population based cross sectional study. *Arch Dis Child*, 88(8), 671-675.

Azar, S.T., Tamim, H., Beyhum, H.N., Zouhair Habbal, M., & Almawi, W.Y. (1999). Type I (insulin-dependent) diabetes is a Th1- and Th2-mediated autoimmune disease. *Clinical and Diagnostic Laboratory Immunology*, 6(3), 306-310.

Bach, J.F. (2005). Infections and autoimmune diseases. *J Autoimmun*, 25 Suppl, 74-80.

Ball, T.M., Castro-Rodriguez, J.A., Griffith, K.A., Holberg, C.J., Martinez, F.D., & Wright, A.L. (2000). Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*, 343(8), 538-543.

Bandolier (2005a). Glucose monitoring in type-2 diabetes. *Bandolier*, 132(2).

Bandolier (2005b). Urine glucose testing is a waste of time. *Bandolier*, 134(3).

Barker, D.J., Gardner, M.J., & Power, C. (1982). Incidence of diabetes amongst people aged 18-50 years in nine British towns: a collaborative study. *Diabetologia*, 22(6), 421-425.

Barnett, T. (1998). *The insulin treatment of diabetes: A practical guide*: EMAP Healthcare

Beck-Nielsen, H., & Hother-Nielsen, O. (2004). Obesity in Type 2 Diabetes Mellitus. In D. LeRoith,S.I. Taylor, & J.M. Olefsky (Eds.), *Diabetes Mellitus: A Fundamental and Clinical Text* (pp. pp.857-868): Lippincott Williams & Wilkins.

Bell, J.I., & Hockaday, T.D.R. (1996). Diabetes Mellitus. In D.J. Weatherall,J.G.G. Ledingham, & D.A. Warrell (Eds.), *Oxford Textbook of Medicine* (pp. 1448-1504).

Ben-Shlomo, Y., White, I.R., & Marmot, M. (1996). Does the variation in the socioeconomic characteristics of an area affect mortality? *British Medical Journal*, 312(7037), 1013-1014.

Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*, 31(2), 285-293.

Benach, J., Yasui, Y., Borrell, C., Saez, M., & Pasarin, M.I. (2001). Material deprivation and leading causes of death by gender: Evidence from a nationwide small area study. *Journal of Epidemiology and Community Health*, 55(4), 239-245.

Bennett, P.H., Knowler, W.C., & Rushforth, N.B. (1979). The role of obesity in the development of diabetes in the Pima Indians. In J. Vague, & P.H. Vague (Eds.), *Diabetes and obesity* (p. 117). Amsterdam: Excerpta Medica.

Bentham, G. (1994). Population mixing and sudden infant death syndrome in England and Wales. *Int J Epidemiol*, 23(3), 540-544.

Bhopal, R., Hayes, L., White, M., Unwin, N., Harland, J., Ayis, S., & Alberti, G. (2002). Ethnic and socio-economic inequalities in coronary heart disease, diabetes and risk factors in Europeans and South Asians. *Journal of Public Health Medicine*, 24(2), 95-105.

Billson, H., Pryer, J.A., & Nichols, R. (1999). Variation in fruit and vegetable consumption among adults in Britain. An analysis from the dietary and nutritional survey of British adults. *Eur J Clin Nutr*, 53(12), 946-952.

Bingley, P.J., Douek, I.F., Rogers, C.A., & Gale, E.A. (2000). Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group. *Bmj*, 321(7258), 420-424.

Blom, L., Dahlquist, G., Nystrom, L., Sandstrom, A., & Wall, S. (1989). The Swedish childhood diabetes study--social and perinatal determinants for diabetes in childhood. *Diabetologia*, 32(1), 7-13.

Borch-Johnsen, K., Joner, G., Mandrup-Poulsen, T., Christy, M., Zachau-Christiansen, B., Kastrup, K., & Nerup, J. (1984). Relation between breast-feeding and incidence rates of insulin-dependent diabetes mellitus. A hypothesis. *Lancet*, 2(8411), 1083-1086.

Borrell, L.N., Diez Roux, A.V., Rose, K., Catellier, D., & Clark, B.L. (2004). Neighbourhood characteristics and mortality in the Atherosclerosis Risk in Communities Study. *Int J Epidemiol*, 33(2), 398-407.

Bowling, A., Barber, J., Morris, R., & Ebrahim, S. (2006). Do perceptions of neighbourhood environment influence health? Baseline findings from a British survey of aging. *J Epidemiol Community Health*, 60(6), 476-483.

Boyle, P. (1995). Rural in-migration in England and Wales, 1980-1981. *J Rural Stud*, 11(1), 65-78.

Boyle, P., Norman, P., & Rees, P. (2002). Does migration exaggerate the relationship between deprivation and limiting long-term illness? A Scottish analysis. *Social Science & Medicine*, 55(1), 21-31.

Boyle, P., Exeter, D., & Flowerdew, R. (2004). The role of population change in widening the mortality gap in Scotland. *Area*, 36(2), 164-173.

Boyle, P.J., Gatrell, A.C., & Duke-Williams, O. (1999). The effect on morbidity of variability in deprivation and population stability in England and Wales: an investigation at small-area level. *Soc Sci Med*, 49(6), 791-799.

Boyle, P.J., & Duke-Williams, O. (2004). Does migration exaggerate the relationship between material deprivation and health? In P.J. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The geograhy of health inequalities: views from Britain and North America* (pp. pp. 129-148). London: Ashgate.

Boyle, P.J., Gatrell, A.C., & Duke-Williams, O. (2004). Limiting Long-term Illness and Locality Deprivation in England and Wales: Acknowledging the 'Socio-spatial Context. In P. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geographies of Health Inequality in the Developed World* (pp. 293-308): Ashgate.

Brancati, F.L., Whelton, P.K., Kuller, L.H., & Klag, M.J. (1996). Diabetes mellitus, race, and socioeconomic status. A population-based study. *Ann Epidemiol*, 6(1), 67-73.

Brimblecombe, N., Dorling, D., & Shaw, M. (1999). Mortality and migration in Britain, first results from the British Household Panel Survey. *Social Science & Medicine*, 49(7), 981-988.

Brown, A.F., Ettner, S.L., Piette, J., Weinberger, M., Gregg, E., Shapiro, M.F., Karter, A.J., Safford, M., Waitzfelder, B., Prata, P.A., & Beckles, G.L. (2004). Socioeconomic position and health among persons with diabetes mellitus: a conceptual framework and review of the literature. *Epidemiol Rev*, 26, 63-77.

Brunner, E. (1997). Socioeconomic determinants of health - Stress and the biology of inequality. *British Medical Journal*, 314(7092), 1472-1476.

Brunner, E., & Marmot, M. (1999). Social organisation, stress, and health. In M. Marmot, & R.G. Wilkinson (Eds.), *Social determinants of Health* (pp. 17-43): Oxford University Press.

Bruno, G., Merletti, F., Vuolo, A., Pisu, E., Giorio, M., & Pagano, G. (1993). Sex differences in incidence of IDDM in age-group 15-29 yr. Higher risk in males in Province of Turin, Italy. *Diabetes Care*, 16(1), 133-136.

Campbell, I.W., & Song, S. (2004). Blood Glucose Levels.

Carey, V.J., Walters, E.E., Colditz, G.A., Solomon, C.G., Willett, W.C., Rosner, B.A., Speizer, F.E., & Manson, J.E. (1997). Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am J Epidemiol*, 145(7), 614-619.

Carstairs, V., & Morris, R. (1991). *Deprivation and Health in Scotland*: Aberdeen University Press

Casu, A., Carlini, M., Contu, A., Bottazzo, G.F., & Songini, M. (2000). Type 1 diabetes in sardinia is not linked to nitrate levels in drinking water. *Diabetes Care*, 23(7), 1043-1044.

Ceriello, A., & Motz, E. (2004). Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol*, 24(5), 816-823.

Champion, A.G. (1994). Population change and migration in Britain since 1981: evidence for continuing deconcentration. *Environ Plan A*, 26(10), 1,501-520.

Chaturvedi, N., Jarrett, J., Shipley, M.J., & Fuller, J.H. (1998). Socioeconomic gradient in morbidity and mortality in people with diabetes: cohort study findings from the Whitehall study and the WHO multinational study of vascular disease in diabetes. *British Medical Journal*, 316(7125), 100-105.

Colditz, G.A., Manson, J.E., Stampfer, M.J., Rosner, B., Willett, W.C., & Speizer, F.E. (1992). Diet and risk of clinical diabetes in women. *Am J Clin Nutr*, 55(5), 1018-1023.

Connolly, V., Unwin, N., Sherriff, P., Bilous, R., & Kelly, W. (2000). Diabetes prevalence and socioeconomic status: a population based study showing increased prevalence of type 2 diabetes mellitus in deprived areas. *Journal of Epidemiology and Community Health*, 54(3), 173-177.

Coombes, M.G., Raybould, S.R., Wong, Y.C.L., & Openshaw, S. (1995). Towards an index of deprivation: a review of alternative approaches., *1001 Deprivation Index: A review of approaches and a matirx of results.* London: Department of the Environment, HMSO.

Coster, S., Gulliford, M.C., Seed, P.T., Powrie, J.K., & Swaminathan, R. (2000). Self-monitoring in Type 2 diabetes mellitus: a meta-analysis. *Diabetic Medicine*, 17(11), 755-761.

Court, S., & Lamb, W.H. (1997). *Childhood and adolescent diabetes*: Wiley

Crowley, T.J. (2000). Causes of Climate Change Over the Past 1000 Years. *Science*, 289(5477), 270-277.

Cummins, S., & Macintyre, S. (2002). A systematic study of an urban foodscape: The price and availability of food in Greater Glasgow. *Urban Studies*, 39(11), 2115-2130.

Dabelea, D., & Hamman, R.F. (2004). Epidemiology of Type 2 Diabetes Mellitus. In D. LeRoith,S.I. Taylor, & J.M. Olefsky (Eds.), *Diabetes Mellitus: a fundamental and clinical text*: Lippincott Williams & Wilkins.

Dacou-Voutetakis, C., Karavanaki, K., & Tsoka-Gennatas, H. (1995). National data on the epidemiology of IDDM in Greece. Cases diagnosed in 1992. Hellenic Epidemiology Study Group. *Diabetes Care*, 18(4), 552-554.

Dahl-Jorgensen, K., Joner, G., & Hanssen, K.F. (1991). Relationship between cows' milk consumption and incidence of IDDM in childhood. *Diabetes Care*, 14(11), 1081-1083.

Dahlquist, G., Blom, L., Holmgren, G., Hagglof, B., Larsson, Y., Sterky, G., & Wall, S. (1985). The epidemiology of diabetes in Swedish children 0-14 years--a six-year prospective study. *Diabetologia*, 28(11), 802-808.

Dahlquist, G., & Kallen, B. (1992). Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes mellitus. *Diabetologia*, 35(7), 671-675.

Dahlquist, G. (1993). Etiological aspects of insulin-dependent diabetes mellitus: an epidemiological perspective. *Autoimmunity*, 15(1), 61-65.

Dahlquist, G., & Mustonen, L. (1994). Childhood onset diabetes--time trends and climatological factors. *Int J Epidemiol*, 23(6), 1234-1241.

Dahlquist, G.G., Blom, L.G., Persson, L.A., Sandstrom, A.I., & Wall, S.G. (1990). Dietary factors and the risk of developing insulin dependent diabetes in childhood. *Bmj*, 300(6735), 1302-1306.

Dales, R., Chen, Y., Lin, M., & Karsh, J. (2005). The association between allergy and diabetes in the Canadian population: Implications for the Th1-Th2 hypothesis. *European Journal of Epidemiology*, 20(8), 713-717.

Davey Smith, G., Hart, C., Blane, D., Gillis, C., & Hawthorne, V. (1997). Lifetime socioeconomic position and mortality: prospective observational study. *Bmj*, 314(7080), 547-552.

Davey Smith, G., Hart, C., Watt, G., Hole, D., & Hawthorne, V. (1998). Individual social class, area-based deprivation, cardiovascular disease risk factors, and mortality: the Renfrew and Paisley Study. *J Epidemiol Community Health*, 52(6), 399-405.

Davey Smith, G., Shaw, M., & Dorling, D. (1998). Shrinking areas and mortality. *Lancet*, 352(9138), 1439-1440.

Davey Smith, G., Shaw, M., & Dorling, D. (2001). Population change and mortality in men and women. *J Epidemiol Community Health*, 55(1), 9.

DCCT Research Group (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*, 329(14), 977-986.

Deaton, A. (2003). Health, inequality, and economic development. *Journal of Economic Literature*, 41(1), 113-158.

Denman, A.M., & Rager-Zisman, B. (2004). Viruses and autoimmune diseases - Adapting Koch's postulates. *Autoimmunity Reviews*, 3(5), 355-361.

Diabetes Control and Complications Trial Research Group (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*, 329(14), 977-986.

Diabetes UK (2002). The National Paedatric Diabetes Audit.

Diabetes UK (2004). Diabetes in the UK: A Report from Diabetes UK.

Diabetes UK (2005a). Diabetes: State of the Nation 2005.

Diabetes UK (2005b). Diabetes Affects Record Numbers.

Díaz-Horta, O., Bello, M., Cabrera-Rode, E., Suárez, J., Más, P., García, I., Abalos, I., Jofra, R., Molina, G., Díaz-Díaz, O., & Dimario, U. (2001). Echovirus 4 and type 1 diabetes mellitus. *Autoimmunity*, 34(4), 275-281.

Dolk, H., Pattenden, S., & Johnson, A. (2001). Cerebral palsy, low birthweight and socio-economic deprivation: inequalities in a major cause of childhood disability. *Paediatr Perinat Epidemiol*, 15(4), 359-363.

Drash, A.L., Lipton, R.B., Dorman, J.S., Becker, D.J., LaPorte, R.E., Orchard, T.J., Riley, W.J., Trucco, M., & Kuller, L.H. (1991). The interface between epidemiology and molecular biology in the search for the causes of insulin-dependent diabetes mellitus. *Ann Med*, 23(4), 463-471.

Duggirala, R., Blangero, J., Almasy, L., Dyer, T.D., Williams, K.L., Leach, R.J., O'Connell, P., & Stern, M.P. (1999). Linkage of type 2 diabetes mellitus and of age at onset to a genetic location on chromosome 10q in Mexican Americans. *Am J Hum Genet*, 64(4), 1127-1140.

Dundee City Council (2000). Population Trends: Planning and Tranportation Department.

Ecob, R., & Macintyre, S. (2000). Small area variations in health related behaviours; do these depend on the behaviour itself, its measurement, or on personal characteristics? *Health & Place*, 6(4), 261-274.

Edwards, R., Burns, J.A., McElduff, P., Young, R.J., & New, J.P. (2003). Variations in process and outcomes of diabetes care by socio-economic status in Salford, UK. *Diabetologia*, 46(6), 750-759.

Ehtisham, S., Barrett, T.G., & Shaw, N.J. (2000). Type 2 diabetes mellitus in UK children--an emerging problem. *Diabet Med*, 17(12), 867-871.

Elbein, S.C., Hoffman, M.D., Teng, K., Leppert, M.F., & Hasstedt, S.J. (1999). A genome-wide search for type 2 diabetes susceptibility genes in Utah Caucasians. *Diabetes*, 48(5), 1175-1182.

Ellaway, A., & Macintyre, S. (2003). Play areas for children. *Journal of epidemiology and community health*, 57(5), 315.

Elliott, R.B., & Martin, J.M. (1984). Dietary protein: a trigger of insulin-dependent diabetes in the BB rat? *Diabetologia*, 26(4), 297-299.

EURODIAB (2000). Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. EURODIAB Substudy 2 Study Group. *Diabetologia*, 43(1), 47-53.

European Diabetes Policy Group (1999a). A desktop guide to Type 2 diabetes mellitus. *Diabet Med*, 16(9), 716-730.

European Diabetes Policy Group (1999b). A desktop guide to Type 1 (insulin-dependent) diabetes mellitus. *Diabet Med*, 16(3), 253-266.

Evans, J.M.M., Newton, R.W., Ruta, D.A., MacDonald, T.M., Stevenson, R.J., & Morris, A.D. (1999). Frequency of blood glucose monitoring in relation to glycaemic control: Observational study with diabetes database. *British Medical Journal*, 318(7202), 83-86.

Evans, J.M.M., Newton, R.W., Ruta, D.A., MacDonald, T.M., & Morris, A.D. (2000). Socio-economic status, obesity and prevalence of Type 1 and Type 2 diabetes mellitus. *Diabetic Medicine*, 17(6), 478-480.

Evans, J.M.M., Lawton, J.M., & Morris, A.D. (2004). Final report for research grant RD03/0002637. Living by numbers: Self-monitoring patterns among people with type 2 diabetes. . *Unpublished.*

Exeter, D.J., Boyle, P., Feng, Z., Flowerdew, R., & Schierloh, N. (2005). The creation of 'consistent areas through time' (CATTs) in Scotland, 1981-2001. *Population trends*(119), 28-36.

Fagot-Campagna, A., Narayan, K.M., & Imperatore, G. (2001). Type 2 diabetes in children. *Bmj*, 322(7283), 377-378.

Fava, D., Leslie, R.D., & Pozzilli, P. (1994). Relationship between dairy product consumption and incidence of IDDM in childhood in Italy. *Diabetes Care*, 17(12), 1488-1490.

Filippi, C., & von Herrath, M. (2005). How viral infections affect the autoimmune process leading to type 1 diabetes. *Cell Immunol*, 233(2), 125-132.

Fiscella, K., & Franks, P. (2000). Individual income, income inequality, health, and mortality: What are the relationships? *Health Services Research*, 35(1), 307-318.

Foster, H.D. (1992). *Health, Disease & The Environment* London: Bellhaven Press

Fourouhi, N., Hall, E., & McKeigue, P. (1997). A life course to diabetes. In D. Kuh, & Y. Ben-Shlomo (Eds.), *A life course approach to chronic disease epidemiology.* (pp. pp. 165-188).

Franzini, L., Ribble, J., & Spears, W. (2001). The effects of income inequality and income level on mortality vary by population size in Texas counties. *J Health Soc Behav*, 42(4), 373-387.

Frisk, G., Friman, G., Tuvemo, T., Fohlman, J., & Diderholm, H. (1992). Coxsackie B virus IgM in children at onset of type 1 (insulin-dependent) diabetes mellitus: evidence for IgM induction by a recent or current infection. *Diabetologia*, 35(3), 249-253.

Frisk, G., Nilsson, E., Tuvemo, T., Friman, G., & Diderholm, H. (1992). The possible role of Coxsackie A and echo viruses in the pathogenesis of type I diabetes mellitus studied by IgM analysis. *J Infect*, 24(1), 13-22.

Gallichan, M. (1997). Self monitoring of glucose by people with diabetes: Evidence based practice. *British Medical Journal*, 314(7085), 964-967.

Gamble, D.R., Taylor, K.W., & Cumming, H. (1973). Coxsackie viruses and diabetes mellitus. *Br Med J*, 4(5887), 260-262.

Gamble, D.R. (1980). An epidemiological study of childhood diabetes affecting two or more siblings. *Diabetologia*, 19(4), 341-344.

Gardner, S.G., Bingley, P.J., Sawtell, P.A., Weeks, S., & Gale, E.A. (1997). Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. The Bart's-Oxford Study Group. *Bmj*, 315(7110), 713-717.

Gatling, W., Budd, S., Walters, D., Mullee, M.A., Goddard, J.R., & Hill, R.D. (1998). Evidence of an increasing prevalence of diagnosed diabetes mellitus in the Poole area from 1983 to 1996. *Diabetic Medicine*, 15(12), 1015-1021.

Gatling, W., Guzder, R.N., Turnbull, J.C., Budd, S., & Mullee, M.A. (2001). The Poole Diabetes Study: how many cases of Type 2 diabetes are diagnosed each year during normal health care in a defined community? *Diabetes Research and Clinical Practice*, 53(2), 107-112.

Gatrell, A.C. (1997). Structures of geographical and social space and their consequences for human health. *Geografiska Annaler, Series B: Human Geography*, 79(3), 141-154.

Gatrell, A.C., Berridge, D., Bennett, S., Bostock, L., Thomas, C., Popay, J., & Williams, G. (2004). Local Geographies of Health Inequalities. In P. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geography of Health Inequalities in the Developed World: Views from Britain and North America* (pp. pp.177-198): Ashgate.

Gibbon, C., Smith, T., Egger, P., Betts, P., & Phillips, D. (1997). Early infection and subsequent insulin dependent diabetes. *Arch Dis Child*, 77(5), 384-385.

Goldsby, R.A., Kindt, T.J., & Osborne, B.A. (1999). *Immunology* New York: W.H. Freeman & Company

Gottlieb, M.S. (1979). Diabetes in offspring and siblings of juvenile and maturity-onset-type diabetics. *Journal of Chronic Disorders*, 33, 331-339.

Goyder, E.C., McNally, P.G., & Botha, J.L. (2000). Inequalities in access to diabetes care: evidence from a historical cohort study. *Quality in Health Care*, 9(2), 85-89.

Graham, E., Boyle, P.J., Curtis, S., & Moore, E. (2004). Does place matter in studies of health inequalities? In P.J. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geography of Health Inequalities: Views from Britain and North America.* London: Ashgate.

Gravelle, H., Wildman, J., & Sutton, M. (2002). Income, income inequality and health: what can we learn from aggregate data? *Social Science & Medicine*, 54(4), 577-589.

Green, A., & Patterson, C.C. (2001). Trends in the incidence of childhood-onset diabetes in Europe 1989-1998. *Diabetologia*, 44 Suppl 3, B3-8.

Greenland, S. (2001). Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. *International Journal of Epidemiology*, 30(6), 1343-1350.

Gress, T.W., Nieto, F.J., Shahar, E., Wofford, M.R., & Brancati, F.L. (2000). Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med*, 342(13), 905-912.

Grzywa, M.A., & Sobel, A.K. (1995). Incidence of IDDM in the province of Rzeszow, Poland, 0- to 29-year-old age-group, 1980-1992. *Diabetes Care*, 18(4), 542-544.

Haffner, S.M., Stern, M.P., Mitchell, B.D., Hazuda, H.P., & Patterson, J.K. (1990). Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes*, 39(3), 283-288.

Hales, C.N., Barker, D.J., Clark, P.M., Cox, L.J., Fall, C., Osmond, C., & Winter, P.D. (1991). Fetal and infant growth and impaired glucose tolerance at age 64. *Bmj*, 303(6809), 1019-1022.

Hanis, C.L., Boerwinkle, E., Chakraborty, R., Ellsworth, D.L., Concannon, P., Stirling, B., Morrison, V.A., Wapelhorst, B., Spielman, R.S., Gogolin-Ewens, K.J., Shepard, J.M., Williams, S.R., Risch, N., Hinds, D., Iwasaki, N., Ogata, M., Omori, Y., Petzold, C., Rietzch, H., Schroder, H.E., Schulze, J., Cox, N.J., Menzel, S., Boriraj, V.V., Chen, X., Lim, L.R., Lindner, T., Mereu, L.E., Wang, Y.Q., Xiang, K., Yamagata, K., Yang, Y., & Bell, G.I. (1996). A genome-wide search for human non-insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2. *Nat Genet*, 13(2), 161-166.

Hanson, R.L., Ehm, M.G., Pettitt, D.J., Prochazka, M., Thompson, D.B., Timberlake, D., Foroud, T., Kobes, S., Baier, L., Burns, D.K., Almasy, L., Blangero, J., Garvey, W.T., Bennett, P.H., & Knowler, W.C. (1998). An autosomal genomic scan for loci linked to type II diabetes mellitus and body-mass index in Pima Indians. *Am J Hum Genet*, 63(4), 1130-1138.

Hara, H., Egusa, G., Yamakido, M., & Kawate, R. (1994). The high prevalence of diabetes mellitus and hyperinsulinemia among the Japanese-Americans living in Hawaii and Los Angeles. *Diabetes Res Clin Pract*, 24 Suppl, S37-42.

Harding, J.E. (2001). The nutritional basis of the fetal origins of adult disease. *Int J Epidemiol*, 30(1), 15-23.

Harris, M.I. (1989). Screening for non-insulin dependent diabetes. In K.G.M.M. Alberti, & R.S. Mazze (Eds.), *Current trends in non-insulin dependent diabetes mellitus.* Amsterdam: Elsevier Science Publishers.

Harris, M.I. (2001). Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care*, 24(6), 979-982.

Harrison, L.C., Colman, P.G., Dean, B., Baxter, R., & Martin, F.I. (1985). Increase in remission rate in newly diagnosed type I diabetic subjects treated with azathioprine. *Diabetes*, 34(12), 1306-1308.

Harvey, J.N., Craney, L., & Kelly, D. (2002). Estimation of the prevalence of diagnosed diabetes from primary care and secondary care source data: comparison of record linkage with capture-recapture analysis. *J Epidemiol Community Health*, 56(1), 18-23.

Hattersley, A.T., Beards, F., Ballantyne, E., Appleton, M., Harvey, R., & Ellard, S. (1998). Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet*, 19(3), 268-270.

Haverkos, H.W. (1997). Could the aetiology of IDDM be multifactorial? *Diabetologia*, 40(10), 1235-1240.

Haynes, R., & Gale, S. (2000). Deprivation and poor health in rural areas: inequalities hidden by averages. *Health & Place*, 6(4), 275-285.

Haynes, R., Lovett, A., & Sunnenberg, G. (2003). Potential accessibility, travel time, and consumer choice: geographical variations in general medical practice registrations in Eastern England. *Environment and Planning A*, 35(10), 1733-1750.

Helgason, T., & Jonasson, M.R. (1981). Evidence for a food additive as a cause of ketosis-prone diabetes. *Lancet*, 2(8249), 716-720.

Helgason, T., Ewen, S.W., Ross, I.S., & Stowers, J.M. (1982). Diabetes produced in mice by smoked/cured mutton. *Lancet*, 2(8306), 1017-1022.

Helme, K., Otten, A., & Willems, W. (1980). Islet cell antibodies in children with mumps infection. *Lancet*, 2, 211-212.

Helmrich, S.P., Ragland, D.R., Leung, R.W., & Paffenbarger, R.S., Jr. (1991). Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med*, 325(3), 147-152.

Higgs, G., & White, S. (2000). Alternatives to census-based indicators of social disadvantage in rural communities. *Progress in Planning*, 53, 1-81.

Higgs, G. (2004). A Literature Review of the Use of GIS-Based Measures of Access to Health Care Services. *Health Services & Outcomes Research Methodology*, 5, 125-145.

Honeyman, M.C., Coulson, B.S., Stone, N.L., Gellert, S.A., Goldwater, P.N., Steele, C.E., Couper, J.J., Tait, B.D., Colman, P.G., & Harrison, L.C. (2000). Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes*, 49(8), 1319-1324.

Hoorfar, J., Scott, F.W., & Cloutier, H.E. (1991). Dietary plant materials and development of diabetes in the BB rat. *J Nutr*, 121(6), 908-916.

Horwitz, M.S., Ilic, A., Fine, C., Rodriguez, E., & Sarvetnick, N. (2002). Presented antigen from damaged pancreatic β-cells activates autoreactive T cells in virus-mediated autoimmune diabetes. *Journal of Clinical Investigation*, 109(1), 79-87.

Hsieh, C.C., & Pugh, M.D. (1993). Poverty, income inequality, and violent crime: a meta-analysis of recent aggregate data studies. *Criminal Justice Review*, 18, 182-202.

Hu, F.B., Sigal, R.J., Rich-Edwards, J.W., Colditz, G.A., Solomon, C.G., Willett, W.C., Speizer, F.E., & Manson, J.E. (1999). Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *Jama*, 282(15), 1433-1439.

Hunnicutt, J.W., Hardy, R.W., Williford, J., & McDonald, J.M. (1994). Saturated fatty acid-induced insulin resistance in rat adipocytes. *Diabetes*, 43(4), 540-545.

Hyöty, H., & Taylor, K.W. (2002). The role of viruses in human diabetes. *Diabetologia*, 45(10), 1353-1361.

Illi, S., von Mutius, E., Lau, S., Bergmann, R., Niggemann, B., Sommerfeld, C., & Wahn, U. (2001). Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *Bmj*, 322(7283), 390-395.

International Diabetes Federation (2003). *Diabetes Atlas*

Janeway, C.A. (1997). Immunology relevant to diabetes. In D. Porte Jr., & R.S. Sherwin (Eds.), *Diabetes Mellitus.* London: Prentice Hall.

Joffe, M. (1989). Social inequalities in low birth weight: timing of effects and selective mobility. *Soc Sci Med*, 28(6), 613-619.

Johnston, S.L., & Openshaw, P.J. (2001). The protective effect of childhood infections. *Bmj*, 322(7283), 376-377.

Joint Health Surveys Unit (2001). *Health Survey For England: The Health of Minority Ethnic Groups, 1999* London: The Stationery Office

Jongbloet, P.H., Groenewoud, H.M., Hirasing, R.A., & Van Buuren, S. (1998). Seasonality of birth in patients with childhood diabetes in The Netherlands. *Diabetes Care*, 21(1), 190-191.

Jun, H.S., & Yoon, J.W. (2001). The role of viruses in Type I diabetes: Two distinct cellular and molecular pathogenic mechanisms of virus-induced diabetes in animals. *Diabetologia*, 44(3), 271-285.

Jun, H.S., & Yoon, J.W. (2003). A new look at viruses in type 1 diabetes. *Diabetes/Metabolism Research and Reviews*, 19(1), 8-31.

Kaplan, G.A., Pamuk, E.R., Lynch, J.W., Cohen, R.D., & Balfour, J.L. (1996). Inequality in income and mortality in the United States: Analysis of mortality and potential pathways. *British Medical Journal*, 312(7037), 999-1003.

Kaprio, J., Tuomilehto, J., Koskenvuo, M., Romanov, K., Reunanen, A., Eriksson, J., Stengard, J., & Kesaniemi, Y.A. (1992). Concordance for Type-1 (Insulin-Dependent) and Type-2 (Non-Insulin-Dependent) Diabetes-Mellitus in a Population-Based Cohort of Twins in Finland. *Diabetologia*, 35(11), 1060-1067.

Karjalainen, J., Martin, J.M., Knip, M., Ilonen, J., Robinson, B.H., Savilahti, E., Akerblom, H.K., & Dosch, H.M. (1992). A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus. *N Engl J Med*, 327(5), 302-307.

Karvonen, M., Tuomilehto, J., Libman, I., & LaPorte, R. (1993). A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. World Health Organization DIAMOND Project Group. *Diabetologia*, 36(10), 883-892.

Karvonen, M., Rusanen, J., Sundberg, M., Virtala, E., Çolpaert, A., Naukkarinen, A., & Tuomilehto, J. (1997). Regional differences in the incidence of insulin-dependent diabetes mellitus among children in Finland from 1987 to 1991. Childhood Diabetes in Finland (DiMe) Study Group. *Ann Med*, 29(4), 297-304.

Kaufman, D.L., Erlander, M.G., Clare-Salzler, M., Atkinson, M.A., Maclaren, N.K., & Tobin, A.J. (1992). Autoimmunity to two forms of glutamate decarboxylase in insulin-dependent diabetes mellitus. *Journal of Clinical Investigation*, 89(1), 283-292.

Kawachi, I., Kennedy, B.P., Lochner, K., & Prothrow-Stith, D. (1997). Social capital, income inequality, and mortality. *Am J Public Health*, 87(9), 1491-1498.

Kelso, A. (1995). Th1 and Th2 subsets: paradigms lost? *Immunol Today*, 16(8), 374-379.

Kennedy, B.P., Kawachi, I., & Prothrow-Stith, D. (1996). Income distribution and mortality: cross sectional ecological study of the Robin Hood index in the United States. *Bmj*, 312(7037), 1004-1007.

Kolb, H., & Elliott, R.B. (1994). Increasing incidence of IDDM a consequence of improved hygiene? *Diabetologia*, 37(7), 729.

Koppel, S., & McGuffin, P. (1999). Socio-economic factors that predict psychiatric admissions at a local level. *Psychol Med*, 29(5), 1235-1241.

Kramer, M.S., Barr, R.G., Leduc, D.G., Boisjoly, C., & Pless, I.B. (1985). Infant determinants of childhood weight and adiposity. *J Pediatr*, 107(1), 104-107.

Kramer, U., Heinrich, J., Wjst, M., & Wichmann, H.E. (1999). Age of entry to day nursery and allergy in later childhood. *Lancet*, 353(9151), 450-454.

Kumar, D., Gemayel, N.S., Deapen, D., Kapadia, D., Yamashita, P.H., Lee, M., Dwyer, J.H., Roy-Burman, P., Bray, G.A., & Mack, T.M. (1993). North-American twins with IDDM. Genetic, etiological, and clinical significance of disease concordance according to age, zygosity, and the interval after diagnosis in first twin. *Diabetes*, 42(9), 1351-1363.

Kumar, P., & Clark, M. (1998). *Clinical Medicine: A textbook for medical students and doctors*: W.B.Saunders

Kumari, M., Head, J., & Marmot, M. (2004). Prospective study of social and other risk factors for incidence of type 2 diabetes in the Whitehall II study. *Arch Intern Med*, 164(17), 1873-1880.

Kyvik, K.O., Green, A., & Beck-Nielsen, H. (1995). Concordance Rates of Insulin-Dependent Diabetes-Mellitus - a Population-Based Study of Young Danish Twins. *British Medical Journal*, 311(7010), 913-917.

Lammi, N., Karvonen, M., & Tuomilehto, J. (2005). Do microbes have a causal role in type 1 diabetes? *Med Sci Monit*, 11(3), RA63-69.

Lang, T., & Caraher, M. (1998). Access to healthy foods: part 2. Food poverty and shopping deserts: what are the implications for health promotion policy and practice? *Health Education Journal*, 57, 202–211.

Larranaga, I., Arteagoitia, J.M., Rodriguez, J.L., Gonzalez, F., Esnaola, S., & Pinies, J.A. (2005). Socio-economic inequalities in the prevalence of Type 2 diabetes, cardiovascular risk factors and chronic diabetic complications in the Basque Country, Spain. *Diabetic Medicine*, 22(8), 1047-1053.

Leather, S. (1996). *The making of modern malnutrition; an overview of food poverty in the UK.* London: Caroline Walker Trust

Lee, M.S., Wogensen, L., Shizuru, J., Oldstone, M.B., & Sarvetnick, N. (1994). Pancreatic islet production of murine interleukin-10 does not inhibit immune-mediated tissue destruction. *J Clin Invest*, 93(3), 1332-1338.

Lee, P., & Murie, A. (1999). *Literature Review of Social Exclusion* Edinburgh: Stationary Office

Leiter, E.H., Serreze, D.V., & Prochazka, M. (1990). The genetics and epidemiology of diabetes in NOD mice. *Immunol Today*, 11(5), 147-149.

Leslie, R.D., & Elliott, R.B. (1994). Early environmental events as a cause of IDDM. Evidence and implications. *Diabetes*, 43(7), 843-850.

Liu, S., Manson, J.E., Stampfer, M.J., Hu, F.B., Giovannucci, E., Colditz, G.A., Hennekens, C.H., & Willett, W.C. (2000). A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health*, 90(9), 1409-1415.

Lobstein, T., & Leach, R. (2004). Diabetes may be undetected in many children in the UK. *Bmj*, 328(7450), 1261-1262.

Long, S.D., O'Brien, K., MacDonald, K.G., Jr., Leggett-Frazier, N., Swanson, M.S., Pories, W.J., & Caro, J.F. (1994). Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes. A longitudinal interventional study. *Diabetes Care*, 17(5), 372-375.

Lundstrom, R.E., Mordes, J.P., & Rossini, A.A. (1998). The Healing Handbook for Persons with Diabetes.

Lynch, J.W., Kaplan, G.A., Pamuk, E.R., Cohen, R.D., Heck, K.E., Balfour, J.L., & Yen, I.H. (1998). Income inequality and mortality in metropolitan areas of the United States. *American Journal of Public Health*, 88(7), 1074-1080.

Macintyre, S., & Ellaway, A. (1998). Social and local variations in the use of urban neighbourhoods: a case study in Glasgow. *Health Place*, 4(1), 91-94.

Macintyre, S., Ellaway, A., & Cummins, S. (2002). Place effects on health: how can we conceptualise, operationalise and measure them? *Social Science & Medicine*, 55(1), 125-139.

Macintyre, S., McKay, L., Cummins, S., & Burns, C. (2005). Out-of-home food outlets and area deprivation: case study in Glasgow, UK. *Int J Behav Nutr Phys Act*, 2, 16.

Maclaren, N.K., & Atkinsson, M.A. (1997). Insulin-dependent diabetes mellitus: The hypothesis of molecular mimicry between islet cell antigens and microorganisms. *Molecular Medicine Today*, 3(2), 76-83.

Mahtani, M.M., Widen, E., Lehto, M., Thomas, J., McCarthy, M., Brayer, J., Bryant, B., Chan, G., Daly, M., Forsblom, C., Kanninen, T., Kirby, A., Kruglyak, L., Munnelly, K., Parkkonen, M., Reeve-Daly, M.P., Weaver, A., Brettin, T., Duyk, G., Lander, E.S., & Groop, L.C. (1996). Mapping of a gene for type 2 diabetes associated with an insulin secretion defect by a genome scan in Finnish families. *Nat Genet*, 14(1), 90-94.

Manson, J.E., Rimm, E.B., Stampfer, M.J., Colditz, G.A., Willett, W.C., Krolewski, A.S., Rosner, B., Hennekens, C.H., & Speizer, F.E. (1991). Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet*, 338(8770), 774-778.

Marmot, M.G., Smith, G.D., Stansfeld, S., Patel, C., North, F., Head, J., White, I., Brunner, E., & Feeney, A. (1991). Health inequalities among British civil servants: the Whitehall II study. *Lancet*, 337(8754), 1387-1393.

Martin, S., Schneider, B., Heinemann, L., Lodwig, V., Kurth, H.J., Kolb, H., Scherbaum, W., & ROSSO Study Grp (2006). Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. *Diabetologia*, 49(2), 271-278.

Mather, H.M., & Keen, H. (1985). The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans. *Br Med J (Clin Res Ed)*, 291(6502), 1081-1084.

McAlpine, R., & Cunningham, S. (2004). Managed Clinical Network Outcomes Report.

McEvoy, R., Cooper, L., Rubinstein, P., Fedun, B., & Ginsberg-Felner, F. (1986). Type 1 diabetes mellitus (IDDM) and autoimmunity in patients with congenital rubella syndrome (CRS): increased incidence of insulin autoantibodies. *Diabetes*, 35, 187A.

McFarland, H.F. (1996). Complexities in the treatment of autoimmune disease. *Science*, 274(5295), 2037-2038.

McKinney, P.A., Law, G.R., Bodansky, H.J., Staines, A., & Williams, D.R. (1996). Geographical mapping of childhood diabetes in the northern English county of Yorkshire. *Diabet Med*, 13(8), 734-740.

McKinney, P.A., Okasha, M., Parslow, R.C., Law, G.R., Gurney, K.A., Williams, R., & Bodansky, H.J. (2000). Early social mixing and childhood Type 1 diabetes mellitus: a case-control study in Yorkshire, UK. *Diabet Med*, 17(3), 236-242.

McLafferty, S.L. (2003). GIS and health care. *Annual Review of Public Health*, 24, 25-42.

Meadows, P. (1995). Variation of Diabetes-Mellitus Prevalence in General-Practice and Its Relation to Deprivation. *Diabetic Medicine*, 12(8), 696-700.

Medici, F., Hawa, M., Ianari, A., Pyke, D.A., & Leslie, R.D. (1999). Concordance rate for type II diabetes mellitus in monozygotic twins: actuarial analysis. *Diabetologia*, 42(2), 146-150.

Mertens, T., Gruneklee, D., & Eggers, H.J. (1983). Neutralizing antibodies against Coxsackie B viruses in patients with recent onset of type I diabetes. *Eur J Pediatr*, 140(4), 293-294.

Miyazaki, I., Cheung, R.K., Gaedigk, R., Hui, M.F., Van der Meulen, J., Rajotte, R.V., & Dosch, H.M. (1995). T cell activation and anergy to islet cell antigen in type I diabetes. *J Immunol*, 154(3), 1461-1469.

Molarius, A., & Janson, S. (2000). Population change and mortality in men and women. *J Epidemiol Community Health*, 54(10), 772.

Morris, A.D., Boyle, D.I.R., MacAlpine, R., Emslie-Smith, A., Jung, R.T., Newton, R.W., & MacDonald, T.M. (1997). The diabetes audit and research in Tayside

Scotland (DARTS) study: electronic record linkage to create a diabetes register. *British Medical Journal*, 315(7107), 524-528.

Mosmann, T.R., Cherwinski, H., Bond, M.W., Giedlin, M.A., & Coffman, R.L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol*, 136(7), 2348-2357.

Müller-Wieland, D., Kotzka, J., & Goldstein, B.J. (2003). Pathogenesis of type 2 diabetes. In B.J. Goldsteing, & D. Müller-Wieland (Eds.), *Textbook of Type 2 Diabetes.* London: Martin Dunitz.

Neel, J.V. (1999). Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? 1962. *Bull World Health Organ*, 77(8), 694-703; discussion 692-693.

NHS National Prescribing Centre (2002). When and how should patients with diabetes mellitus test blood glucose? *MeReC Bulletin*, 13(1), 1-4.

Nicholl, C.G., Levy, J.C., Mohan, V., Rao, P.V., & Mather, H.M. (1986). Asian diabetes in Britain: a clinical profile. *Diabet Med*, 3(3), 257-260.

Norman, P., Boyle, P., & Rees, P. (2005). Selective migration, health and deprivation: a longitudinal analysis. *Social Science & Medicine*, 60(12), 2755-2771.

O'Reilly, D. (1994). Health and social inequality in Europe. Migration from deprived areas may be a factor. *Bmj*, 309(6946), 57-58.

O'Reilly, D., Browne, S., Johnson, Z., & Kelly, A. (2001). Are cities becoming more unhealthy? An analysis of mortality rates in Belfast and Dublin between 1981 and 1991 to illustrate a methodological difficulty with ecological studies. *J Epidemiol Community Health*, 55(5), 354-355.

Office for National Statistics (2000). *Key Health Statistics for General Practice.* London: The Stationery Office

Office of the Chief Statistician (2004). Scottish Index of Multiple Deprivation: Scottish Executive.

Ohlson, L.O., Larsson, B., Svardsudd, K., Welin, L., Eriksson, H., Wilhelmsen, L., Bjorntorp, P., & Tibblin, G. (1985). The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes*, 34(10), 1055-1058.

Olesen, A.B., Juul, S., Birkebaek, N., & Thestrup-Pedersen, K. (2001). Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study. *Lancet*, 357(9270), 1749-1752.

Onkamo, P., Vaananen, S., Karvonen, M., & Tuomilehto, J. (1999). Worldwide increase in incidence of Type I diabetes - The analysis of the data on published incidence trends. *Diabetologia*, 42(12), 1395-1403.

Openshaw, S. (1984). The Modifiable Areal Unit Problem., *Concepts and Techniques in Modern Geography Number 38.* Norwich: Geobooks.

Pak, C.Y., Eun, H.M., McArthur, R.G., & Yoon, J.W. (1988). Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet*, 2(8601), 1-4.

Parker, E.B., & Campbell, J.L. (1998). Measuring access to primary medical care: some examples of the use of geographical information systems. *Health & Place*, 4(2), 183-193.

Parslow, R.C., McKinney, P.A., Law, G.R., Staines, A., Williams, R., & Bodansky, H.J. (1997). Incidence of childhood diabetes mellitus in Yorkshire, northern England, is associated with nitrate in drinking water: An ecological analysis. *Diabetologia*, 40(5), 550-556.

Parslow, R.C., McKinney, P.A., Law, G.R., & Bodansky, H.J. (2001). Population mixing and childhood diabetes. *Int J Epidemiol*, 30(3), 533-538; discussion 538-539.

Passa, P. (2002). Diabetes trends in Europe. *Diabetes-Metabolism Research and Reviews*, 18, S3-S8.

Patterson, C.C., Smith, P.G., Webb, J., Heasman, M.A., & Mann, J.I. (1988). Geographical variation in the incidence of diabetes mellitus in Scottish children during the period 1977-1983. *Diabet Med*, 5(2), 160-165.

Patterson, C.C., & Waugh, N.R. (1992). Urban/rural and deprivational differences in incidence and clustering of childhood diabetes in Scotland. *Int J Epidemiol*, 21(1), 108-117.

Patterson, C.C., Carson, D.J., Hadden, D.R., Waugh, N.R., & Cole, S.K. (1994). A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. *Diabetes Care*, 17(5), 376-381.

Patterson, C.C., Carson, D.J., & Hadden, D.R. (1996). Epidemiology of childhood IDDM in Northern Ireland 1989-1994: low incidence in areas with highest population density and most household crowding. Northern Ireland Diabetes Study Group. *Diabetologia*, 39(9), 1063-1069.

Patterson, K., Chandra, R.S., & Jenson, A.B. (1981). Congenital rubella, insulitis, and diabetes mellitus in an infant. *Lancet*, 1(8228), 1048-1049.

Pennline, K.J., Roque-Gaffney, E., & Monahan, M. (1994). Recombinant human IL-10 prevents the onset of diabetes in the nonobese diabetic mouse. *Clin Immunol Immunopathol*, 71(2), 169-175.

Perry, B., & Gesler, W. (2000). Physical access to primary health care in Andean Bolivia. *Social Science & Medicine*, 50(9), 1177-1188.

Pettitt, D.J., Forman, M.R., Hanson, R.L., Knowler, W.C., & Bennett, P.H. (1997). Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. *Lancet*, 350(9072), 166-168.

Phillimore, P., Beattie, A., & Townsend, P. (1994). Widening inequality of health in northern England, 1981-91. *Bmj*, 308(6937), 1125-1128.

Phillips, R.L., Kinman, E.L., Schnitzer, P.G., Lindbloom, E.J., & Ewigman, B. (2000). Using geographic information systems to understand health care access. *Archives of Family Medicine*, 9(10), 971-978.

Phipps, K., Barker, D.J., Hales, C.N., Fall, C.H., Osmond, C., & Clark, P.M. (1993). Fetal growth and impaired glucose tolerance in men and women. *Diabetologia*, 36(3), 225-228.

Pickett, K.E., & Pearl, M. (2001). Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. *J Epidemiol Community Health*, 55(2), 111-122.

Pickett, K.E., Kelly, S., Brunner, E., Lobstein, T., & Wilkinson, R.G. (2005). Wider income gaps, wider waistbands? An ecological study of obesity and income inequality. *J Epidemiol Community Health*, 59(8), 670-674.

Poulsen, P., Kyvik, K.O., Vaag, A., & Beck-Nielsen, H. (1999). Heritability of type II (non-insulin-dependent) diabetes mellitus and abnormal glucose tolerance--a population-based twin study. *Diabetologia*, 42(2), 139-145.

Pundziute-Lycka, A., Urbonaite, B., & Dahlquist, G. (2000). Infections and risk of Type I (insulin-dependent) diabetes mellitus in Lithuanian children. *Diabetologia*, 43(10), 1229-1234.

Rangasami, J.J., Greenwood, D.C., McSporran, B., Smail, P.J., Patterson, C.C., & Waugh, N.R. (1997). Rising incidence of type 1 diabetes in Scottish children, 1984-93. The Scottish Study Group for the Care of Young Diabetics. *Arch Dis Child*, 77(3), 210-213.

Rapoport, M.J., Jaramillo, A., Zipris, D., Lazarus, A.H., Serreze, D.V., Leiter, E.H., Cyopick, P., Danska, J.S., & Delovitch, T.L. (1993). Interleukin 4 reverses T cell proliferative unresponsiveness and prevents the onset of diabetes in nonobese diabetic mice. *J Exp Med*, 178(1), 87-99.

Regidor, E., Calle, M.E., Dominguez, V., & Navarro, P. (2002). Inequalities in mortality in shrinking and growing areas. *J Epidemiol Community Health*, 56(12), 919-921.

Revil, J. (2003). UK faces child diabetes epidemic: Obesity and lack of exercise to blame, *The Observer*.

Rewers, M., LaPorte, R.E., Walczak, M., Dmochowski, K., & Bogaczynska, E. (1987). Apparent epidemic of insulin-dependent diabetes mellitus in Midwestern Poland. *Diabetes*, 36(1), 106-113.

Reynolds, R.M., & Strachan, M.W. (2004). Home blood glucose monitoring in type 2 diabetes. *British Medical Journal*, 329(7469), 754-755.

Robbins, J.M., Vaccarino, V., Zhang, H., & Kasl, S.V. (2005). Socioeconomic status and diagnosed diabetes incidence. *Diabetes Res Clin Pract*, 68(3), 230-236.

Robinson, N., Yateman, N.A., Protopapa, L.E., & Bush, L. (1990). Employment problems and diabetes. *Diabet Med*, 7(1), 16-22.

Roivainen, M., Rasilainen, S., Ylipaasto, P., Nissinen, R., Ustinov, J., Bouwens, L., Eizirik, D.L., Hovi, T., & Otonkoski, T. (2000). Mechanisms of coxsackievirus-induced damage to human pancreatic ?-cells. *Journal of Clinical Endocrinology and Metabolism*, 85(1), 432-440.

Roper, N.A., Bilous, R.W., Kelly, W.F., Unwin, N.C., & Connolly, V.M. (2001). Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population based study. *British Medical Journal*, 322(7299), 1389-1393.

Rosero-Bixby, L. (2004). Spatial access to health care in Costa Rica and its equity: a GIS-based study. *Social Science & Medicine*, 58(7), 1271-1284.

Ross, N.A., Wolfson, M.C., Dunn, J.R., Berthelot, J.M., Kaplan, G.A., & Lynch, J.W. (2000). Relation between income inequality and mortality in Canada and in the United States: cross sectional assessment using census data and vital statistics. *Bmj*, 320(7239), 898-902.

Rothwell, P.M., Staines, A., Smail, P., Wadsworth, E., & McKinney, P. (1996). Seasonality of birth of patients with childhood diabetes in Britain. *Bmj*, 312(7044), 1456-1457.

Rothwell, P.M., Gutnikov, S.A., McKinney, P.A., Schober, E., Ionescu-Tirgoviste, C., & Neu, A. (1999). Seasonality of birth in children with diabetes in Europe: multicentre cohort study. European Diabetes Study Group. *Bmj*, 319(7214), 887-888.

Rural Development Comittee (2003). Inquiry into Integrated Rural Development. Volume 2: Evidence.

Salmeron, J., Hu, F.B., Manson, J.E., Stampfer, M.J., Colditz, G.A., Rimm, E.B., & Willett, W.C. (2001). Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr*, 73(6), 1019-1026.

Samuelsson, U., Johansson, C., Carstensen, J., & Ludvigsson, J. (1994). Space-time clustering in insulin-dependent diabetes mellitus (IDDM) in south-east Sweden. *Int J Epidemiol*, 23(1), 138-142.

Sanmartin, C., Ross, N.A., Tremblay, S., Wolfson, M., Dunn, J.R., & Lynch, J. (2003). Labour market income inequality and mortality in North American metropolitan areas. *J Epidemiol Community Health*, 57(10), 792-797.

Sargeant, L.A., Khaw, K.T., Bingham, S., Day, N.E., Luben, R.N., Oakes, S., Welch, A., & Wareham, N.J. (2001). Cigarette smoking and glycaemia: the EPIC-Norfolk Study. European Prospective Investigation into Cancer. *Int J Epidemiol*, 30(3), 547-554.

Savilahti, E., Ormala, T., Saukkonen, T., Sandini-Pohjavuori, U., Kantele, J.M., Arato, A., Ilonen, J., & Akerblom, H.K. (1999). Jejuna of patients with insulin-dependent diabetes mellitus (IDDM) show signs of immune activation. *Clin Exp Immunol*, 116(1), 70-77.

Schopfer, K., Matter, L., Flueler, U., & Werder, E. (1982). Diabetes mellitus, endocrine autoantibodies, and prenatal rubella infection. *Lancet*, 2(8290), 159.

Schwimmbeck, P.L., Dyrberg, T., & Oldstone, M.B. (1988). Abrogation of diabetes in BB rats by acute virus infection. Association of viral-lymphocyte interactions. *J Immunol*, 140(10), 3394-3400.

Scott, F.W., Sarwar, G., & Cloutier, H.E. (1988). Diabetogenicity of various protein sources in the diet of the diabetes-prone BB rat. *Adv Exp Med Biol*, 246, 277-285.

Scott, F.W. (1990). Cow milk and insulin-dependent diabetes mellitus: is there a relationship? *Am J Clin Nutr*, 51(3), 489-491.

Scottish Diabetes Survey Monitoring Group (2004). Scottish Diabetes Survey 2003. Edinburgh: Scottish Executive.

Scottish Economic Research (2006). Labour Market Statistics – April 2006.

Scottish Executive (2001). Right Medicine: A Strategy for Pharmaceutical Care in Scotland.

Sharma, A.M. (1998). The thrifty-genotype hypothesis and its implications for the study of complex genetic disorders in man. *J Mol Med*, 76(8), 568-571.

Shaw, M., Dorling, D., Gordon, D., & Davey Smith, G. (2004). The widening gap - health inequalities in Britain at the end of the twentieth century. In P.J. Boyle,S. Curtis,E. Graham, & E. Moore (Eds.), *The Geographies of Health Inequalities in the Developed World* (pp. pp. 77-100). London: Ashgate.

Sheikh, A., Smeeth, L., & Hubbard, R. (2003). There is no evidence of an inverse relationship between T(H)2-mediated atopy and T(H)1-mediated autoimmune disorders: Lack of support for the hygiene hypothesis. *Journal of Allergy and Clinical Immunology*, 111(1), 131-135.

Sibley, R.K., Sutherland, D.E., Goetz, F., & Michael, A.F. (1985). Recurrent diabetes mellitus in the pancreas iso- and allograft. A light and electron microscopic and immunohistochemical analysis of four cases. *Lab Invest*, 53(2), 132-144.

Silink, M., Kida, K., & Rosenbloom, A.L. (2003). Global evolution of diabetes in children and adolescents. In M. Silink,K. Kida, & A. Rosenbloom (Eds.), *Type 2 Diabetes in Childhood and Adolescence: A Global Perspective* (pp. pp.1-8). London: Martin Dunitz.

Simmons, D., Williams, D.R., & Powell, M.J. (1991). The Coventry Diabetes Study: prevalence of diabetes and impaired glucose tolerance in Europids and Asians. *Q J Med*, 81(296), 1021-1030.

Skarsvik, S., Puranen, J., Honkanen, J., Roivainen, M., Ilonen, J., Holmberg, H., Ludvigsson, J., & Vaarala, O. (2006). Decreased in vitro type 1 immune response against coxsackie virus B4 in children with type 1 diabetes. *Diabetes*, 55(4), 996-1003.

Sloggett, A., & Joshi, H. (1994). Higher Mortality in Deprived Areas - Community or Personal Disadvantage. *British Medical Journal*, 309(6967), 1470-1474.

Songini, M., Bernardinelli, L., Clayton, D., Montomoli, C., Pascutto, C., Ghislandi, M., Fadda, D., & Bottazzo, G.F. (1998). The Sardinian IDDM study: 1. Epidemiology and geographical distribution of IDDM in Sardinia during 1989 to 1994. *Diabetologia*, 41(2), 221-227.

Stafford, M., & Marmot, M. (2003). Neighbourhood deprivation and health: does it affect us all equally? *Int J Epidemiol*, 32(3), 357-366.

Stafford, M., Martikainen, P., Lahelma, E., & Marmot, M. (2004). Neighbourhoods and self rated health: a comparison of public sector employees in London and Helsinki. *J Epidemiol Community Health*, 58(9), 772-778.

Staines, A., Bodansky, H.J., Lilley, H.E., Stephenson, C., McNally, R.J., & Cartwright, R.A. (1993). The epidemiology of diabetes mellitus in the United Kingdom: the Yorkshire Regional Childhood Diabetes Register. *Diabetologia*, 36(12), 1282-1287.

Staines, A., Bodansky, H.J., McKinney, P.A., Alexander, F.E., McNally, R.J., Law, G.R., Lilley, H.E., Stephenson, C., & Cartwright, R.A. (1997). Small area variation in the incidence of childhood insulin-dependent diabetes mellitus in Yorkshire, UK: links with overcrowding and population density. *Int J Epidemiol*, 26(6), 1307-1313.

Stewart, D., McCaig, D., Davie, A., Juroszek, L., Blackwood, L., Findlay, N., & McCarthy, S. (2004). Glucose self-monitoring in primary care: a survey of current practice. *Journal of Clinical Pharmacy and Therapeutics*, 29(3), 273-277.

Stiller, C.A., & Boyle, P.J. (1996). Effect of population mixing and socioeconomic status in England and Wales, 1979-85, on lymphoblastic leukaemia in children. *Bmj*, 313(7068), 1297-1300.

Strachan, D.P. (1989). Hay fever, hygiene, and household size. *Bmj*, 299(6710), 1259-1260.

Subramanian, S.V., & Kawachi, I. (2004). Income inequality and health: what have we learned so far? *Epidemiol Rev*, 26, 78-91.

Swinburn, B.A., Nyomba, B.L., Saad, M.F., Zurlo, F., Raz, I., Knowler, W.C., Lillioja, S., Bogardus, C., & Ravussin, E. (1991). Insulin resistance associated with lower rates of weight gain in Pima Indians. *J Clin Invest*, 88(1), 168-173.

Szreter, S. (1996). *Fertility, Class and Gender on Britain 1860-1940* Cambridge: Cambridge University Press

Tang, M., Chen, Y., & Krewski, D. (2003). Gender-related differences in the association between socioeconomic status and self-reported diabetes. *Int J Epidemiol*, 32(3), 381-385.

Tarn, A.C., Thomas, J.M., Dean, B.M., Ingram, D., Schwarz, G., Bottazzo, G.F., & Gale, E.A. (1988). Predicting insulin-dependent diabetes. *Lancet*, 1(8590), 845-850.

Tillil, H., & Kobberling, J. (1987). Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients. *Diabetes*, 36(1), 93-99.

Townsend, P. (1979). *Poverty in the United Kingdom* London: Penguin

Townsend, P., Phillimore, P., & Beattie, A. (1988). *Health and deprivation: inequality and the North* London: Croom Helm

UK Prospective Diabetes Study Group (1988). UK Prospective Diabetes Study. IV. Characteristics of newly presenting type 2 diabetic patients: male preponderance and obesity at different ages. Multi-center Study. *Diabet Med*, 5(2), 154-159.

UK Prospective Diabetes Study Group (1998a). Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. *Bmj*, 317(7160), 720-726.

UK Prospective Diabetes Study Group (1998b). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, 352(9131), 837-853.

UK Prospective Diabetes Study Group (1998c). Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *Bmj*, 317(7160), 713-720.

UK Prospective Diabetes Study Group (1998d). Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *Bmj*, 317(7160), 703-713.

Vaarala, O., Klemetti, P., Savilahti, E., Reijonen, H., Ilonen, J., & Akerblom, H.K. (1996). Cellular immune response to cow's milk beta-lactoglobulin in patients with newly diagnosed IDDM. *Diabetes*, 45(2), 178-182.

Vaarala, O., Knip, M., Paronen, J., Hamalainen, A.M., Muona, P., Vaatainen, M., Ilonen, J., Simell, O., & Akerblom, H.K. (1999). Cow's milk formula feeding induces primary immunization to insulin in infants at genetic risk for type 1 diabetes. *Diabetes*, 48(7), 1389-1394.

Valdez, R., Athens, M.A., Thompson, G.H., Bradshaw, B.S., & Stern, M.P. (1994). Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia*, 37(6), 624-631.

Verge, C.F., Silink, M., & Howard, N.J. (1994). The incidence of childhood IDDM in New South Wales, Australia. *Diabetes Care*, 17(7), 693-696.

Verge, C.F., Gianani, R., Yu, L., Pietropaolo, M., Smith, T., Jackson, R.A., Soeldner, J.S., & Eisenbarth, G.S. (1995). Late progression to diabetes and evidence for chronic beta-cell autoimmunity in identical twins of patients with type I diabetes. *Diabetes*, 44(10), 1176-1179.

Virtanen, S.M., Rasanen, L., Aro, A., Ylonen, K., Lounamaa, R., Akerblom, H.K., & Tuomilehto, J. (1994). Is children's or parents' coffee or tea consumption associated with the risk for type 1 diabetes mellitus in children? Childhood Diabetes in Finland Study Group. *Eur J Clin Nutr*, 48(4), 279-285.

von Kries, R., Koletzko, B., Sauerwald, T., von Mutius, E., Barnert, D., Grunert, V., & von Voss, H. (1999). Breast feeding and obesity: cross sectional study. *Bmj*, 319(7203), 147-150.

Wadsworth, E.J., Shield, J.P., Hunt, L.P., & Baum, J.D. (1997). A case-control study of environmental factors associated with diabetes in the under 5s. *Diabet Med*, 14(5), 390-396.

Waldman, R.J. (1992). Income distribution and child mortality. *Quarterly journal of Economics*, 107, 1283-1302.

Waugh, N.R. (1986). Insulin-dependent diabetes in a Scottish region: incidence and urban/rural differences. *J Epidemiol Community Health*, 40(3), 240-243.

Weich, S., Twigg, L., Lewis, G., & Jones, K. (2005). Geographical variation in rates of common mental disorders in Britain: prospective cohort study. *Br J Psychiatry*, 187, 29-34.

Wen, M., Browning, C.R., & Cagney, K.A. (2003). Poverty, affluence, and income inequality: neighborhood economic structure and its implications for health. *Soc Sci Med*, 57(5), 843-860.

West, K.M., & Kalbfleisch, J.M. (1971). Influence of nutritional factors on prevalence of diabetes. *Diabetes*, 20(2), 99-108.

Whatley, C.A. (1992). The remaking of Juteopolis, *Proceedings of Octocentenary Conference*: Abertay Historical Society Publication.

Whitford, D.L., Griffin, S.J., & Prevost, A.T. (2003). Influences on the variation in prevalence of type 2 diabetes between general practices: practice, patient or socioeconomic factors? *British Journal of General Practice*, 53(486), 9-14.

WHO (1999). Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications - Part 1: Diagnosis and Classification of Diabetes Mellitus.

Wilberz, S., Partke, H.J., Dagnaes-Hansen, F., & Herberg, L. (1991). Persistent MHV (mouse hepatitis virus) infection reduces the incidence of diabetes mellitus in non-obese diabetic mice. *Diabetologia*, 34(1), 2-5.

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global prevalence of diabetes - Estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27(5), 1047-1053.

Wilkinson, R.G. (1992). For Debate - Income-Distribution and Life Expectancy. *British Medical Journal*, 304(6820), 165-168.

Wilkinson, R.G. (1996). *Unhealthy Societies: the Affliction of Inequality* London: Routledge

Wilkinson, R.G. (1999). Putting the picture together: prosperity, redistribution health and welfare. In M. Marmot, & R.G. Wilkinson (Eds.), *Social determinants of Health* (pp. 256-274): Oxford University Press.

Wilkinson, R.G. (2006). The Impact of Inequality: Empirical Evidence. *Renewal*, 14.

Wilkinson, R.G., & Pickett, K.E. (2006). Income inequality and population health: a review and explanation of the evidence. *Soc Sci Med*, 62(7), 1768-1784.

Will, J.C., Galuska, D.A., Ford, E.S., Mokdad, A., & Calle, E.E. (2001). Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol*, 30(3), 540-546.

Williams, D.R., Wareham, N.J., Brown, D.C., Byrne, C.D., Clark, P.M., Cox, B.D., Cox, L.J., Day, N.E., Hales, C.N., Palmer, C.R., & et al. (1995). Undiagnosed glucose intolerance in the community: the Isle of Ely Diabetes Project. *Diabet Med*, 12(1), 30-35.

Willliams, G., & Pickup, J. (2004). *Handbook of Diabetes* Massachusetts: Blackwell Publishing

Wong, S., Guerder, S., Visintin, I., Reich, E.P., Swenson, K.E., Flavell, R.A., & Janeway, C.A., Jr. (1995). Expression of the co-stimulator molecule B7-1 in pancreatic beta-cells accelerates diabetes in the NOD mouse. *Diabetes*, 44(3), 326-329.

Yen, I.H., & Kaplan, G.A. (1999). Neighborhood social environment and risk of death: Multilevel evidence from the Alameda County Study. *American Journal of Epidemiology*, 149(10), 898-907.

Yoon, J.W., & Jun, H.S. (2000). Role of Viruses in the Pathogenesis of Type 1 Diabetes Mellitus. In D. LeRoith,S.I. Taylor, & J.M. Plefsky (Eds.), *Diabetes Mellitus: A Fundamental and Clinical Text*: Lippincott, Williams & Wilkins.

Yorkshire & Humber Public Health Laboratory (2005). PBS Diabetes Population Prevalence Model.

Zhao, H., Demaine, A.G., & Millward, B.A. (2000). Seasonality of birth in children with diabetes. Results of various studies differ. *Bmj*, 320(7236), 716.