

TYPE 2 DIABETES IN YOUNGER ADULTS

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Type 2 diabetes in younger adults

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Abstract

Background:

The rising prevalence of obesity and sedentary behaviour has led to a substantial increase in the number of younger adults (<45 years) developing Type 2 diabetes (T2DM). The amount of time spent sitting (sedentary) has been identified as a risk factor for T2DM which, if targeted, has the potential to prevent T2DM.

Aims:

- 1) To extensively phenotype younger adults with T2DM;
- 2) To conduct a systematic review and meta-analysis to investigate the relationship between sedentary time, T2DM, cardiovascular disease, cardiovascular and all-cause mortality;
- 3) To develop the Sedentary Time AND Diabetes (STAND) structured education programme, designed to reduce sedentary time in younger adults at risk of T2DM and use data from the baseline cohort to describe the prevalence of undiagnosed T2DM in this study population;
- 4) To assess the effectiveness of the STAND intervention to reduce sedentary behaviour.

Key findings:

- 1) T2DM in younger adults is associated with an adverse metabolic profile: hyperlipidaemia, vitamin D deficiency, pro-inflammatory state, low physical activity and fitness. Cardiac magnetic resonance imaging demonstrated reduced diastolic strain which was present in the T2DM but not obese or lean control groups.
- 2) Excess sedentary time was positively associated with diabetes, cardiovascular events, cardiovascular mortality and all-cause mortality.
- 3) Previously undiagnosed T2DM was present in 4.7% of 193 participants recruited for the STAND randomised controlled trial.
- 4) The STAND intervention did not significantly reduce sedentary time in the intervention group compared to the control group ($p=0.43$).

Conclusion: This thesis assesses the impact of T2DM on the individual (Chapter Two, Three), quantifies the risk associated with excess sedentary time (Chapter Four) and examines the effectiveness of the STAND programme to reduce sedentary time in younger adults with risk factor for T2DM (Chapters Five to Eight). Recommendations are provided for future research and clinical practice to promote the prevention of T2DM in younger adults.

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List of Abbreviations

BMI = body mass index

CMR = cardiac magnetic resonance imaging

DESMOND = Diabetes Education and Self Management for Ongoing and Newly Diagnosed

GP = general practice/ general practitioner

IPAQ = International Physical Activity Questionnaire

LPL = lipoprotein lipase

LVM = Left ventricular mass

LVMI = Left ventricular mass indexed to body surface area

LVEDV= Left ventricular end diastolic volume

LVEDVI= Left ventricular end diastolic volume indexed to body surface area

LVESV= Left ventricular end systolic volume

LVESV= Left ventricular end systolic volume

MRC = Medical Research Council

MVPA = moderate-to-vigorous physical activity

PREPARE = Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement

RCT = randomised controlled trial

STAND = Sedentary Time ANd Diabetes

T2DM = Type 2 diabetes mellitus

Chapter One: Introduction and guide to the thesis

Western societies are facing an obesity and type 2 diabetes (T2DM) epidemic. T2DM was previously viewed as a disease of the older adult but this condition is being increasingly diagnosed in younger adults (Kitagawa et al. 1998, Dabelea et al. 2009, Braun et al. 1996, Drake et al. 2002). The implications of a diagnosis of T2DM at a young age are far reaching. For the individual there is the increased risk of premature development of renal, cardiac, retinal and neurological complications within the third to fifth decades of life (Dart et al. 2012, Bronson-Castain et al. 2012, Paisey et al. 2009, Rhodes et al. 2012). For society the costs associated with young adults developing incapacitating complications during their working life are substantial. The aetiology of this condition in youth represents a complex interplay between genetic and environmental factors. The majority of younger adults are obese and have a first degree relative with T2DM and many are from minority ethnic groups (Ethisham et al. 2004). Environmental influences such as over-nutrition, physical inactivity, excess sedentary time and social deprivation have all been implicated. The extreme phenotype seen in youth with T2DM culminates in the onset of diabetes complications, more rapidly and more severe than seen in type 1 diabetes (Eppens et al. 2006). We do not yet have a detailed understanding of the long term implications of early onset T2DM but it is likely that outcomes will be devastating for affected individuals.

Preliminary evidence suggests that once early onset T2DM is established, the condition fails to respond to lifestyle or medical interventions as we would anticipate based on existing T2DM data from older adults (Shield et al., 2009, TODAY 2012).

Lifestyle interventions can prevent T2DM and improve glycaemic control in those with T2DM (Knowler et al. 2002, Boule et al. 2001, Gregg et al. 2012). However, the available data from youth with T2DM suggest that this is not the case. Supervised exercise interventions under carefully controlled conditions failed to enhance cardiovascular fitness and cardiometabolic health in younger adults with T2DM while in larger randomised controlled trials, the addition of lifestyle advice to metformin therapy failed to confer benefit (Burns et al. 2007, TODAY 2012). There is a tangible need for a novel and acceptable lifestyle intervention to prevent the development of T2DM in young at risk adults, as once established, management of this condition is extremely challenging.

One possible novel behavioural target in younger people at risk of T2DM is reducing sedentary behaviour. With the availability of multiple energy saving devices such as cars, televisions, computers etc, the average adult now spends 50-70% of their time in sedentary pursuits. The term “sedentary” comes from the Latin *sedere* (“to sit”) and is defined as any waking sitting or lying behaviour with low energy expenditure. The term ‘sedentary behaviour’ refers to sitting/lying behaviour rather than the simple absence of moderate-to-vigorous physical activity (MVPA) (Pate et al. 2008, Sedentary Behaviour Research Network, 2012). While previous public health advice has focused on ensuring adults perform 30 minutes of exercise on most days of the week (Department of Health, 2011), this guidance overlooks the amount of activity performed during the remaining 23.5 hours in each day. Numerous observational studies have identified that excess sedentary time is associated with impaired glucose metabolism and T2DM, metabolic syndrome, cardiovascular disease and mortality (Dunstan et al. 2004, Edwardson et al. 2012, Hu et al. 2003, Stamatakis et

al. 2011, Katzmarzyk et al. 2009). It seems intuitive that if sedentary time is reduced that this will have a positive influence on health outcomes, However, the data to support this hypothesis are currently lacking.

The opportunities for sedentary time are ubiquitous and if sedentary time is harmful, as the observational data suggest, then there is a need to communicate this message to the public. However, we first need robust evidence from randomised controlled trials to demonstrate cause and effect, that reducing sedentary time does indeed confer health benefits. My thesis works towards this aim and an overview of the chapters and their content follows.

Chapters Overview

Chapter Two of this thesis explores the implications of a diagnosis of T2DM at a young age, providing a broad literature review of the topic of T2DM in younger adults (<45 years). Areas covered include the epidemiology, aetiology, pathophysiology, diagnosis, complications, co-morbidities and management. This sets the scene for Chapter Three which also focuses on T2DM in younger adults.

Chapter Three describes the Expedition study, a MRC funded observational study to phenotype 20 young UK adults with T2DM (aged 18-40 years) and compare them with lean and obese controls. A range of outcomes were examined including cardiac magnetic resonance (CMR) imaging, cardio-respiratory fitness, a range of biomedical and anthropometric outcomes. This is one of the first studies to use CMR to assess cardiac structure and function in T2DM and provides an unique insight into the implications of the premature development of T2DM

Chapter Four explores the role of sedentary behaviour in the development of adverse health outcomes including T2DM. In this chapter I present the results of my systematic review and meta-analysis which summarises the available evidence examining the relationship between excess sedentary time and diabetes, cardiovascular disease, cardiovascular and all cause mortality. The findings of this chapter highlight the potentially adverse effects of excess sedentary time and the publication associated with this chapter led to considerable national and international media interest (see Appendix Eight). The findings of this meta-analysis are of primary importance as they were instrumental in shaping and informing the Sedentary Time AND Diabetes (STAND) programme of research which is described in Chapters Five to Eight.

The STAND programme of research is funded by the Medical Research Council National Prevention Research Initiative. The primary hypothesis of the STAND programme is that theory driven group structured education will decrease sedentary behaviour in young adults at risk of T2DM. The secondary hypothesis is that reducing sedentary behaviour will result in favourable changes in key behavioural and biological markers of T2DM risk. The following chapters describe the phases of work underpinning the STAND programme.

Chapter Five describes the first phases of the STAND programme of research. Based on the MRC framework for the development of complex interventions, phases 1 and 2 of STAND describe the feasibility, acceptability, development and piloting of

a theory driven group structured education programme designed to reduce sedentary time in young adults at risk for the development of T2DM.

Chapter Six describes the methodology employed in the STAND randomised controlled trial, designed to test the hypothesis that structured education reduces sedentary time in young adults at risk of T2DM and that such a reduction in sedentary time is associated with improvements in cardio-metabolic health.

Chapter Seven utilises data from the baseline cohort recruited for the STAND randomised controlled trial to describe the prevalence of previously undiagnosed T2DM and impaired glucose metabolism in this high risk cohort. This chapter provides unique data and the findings support the recently published National Institute for Clinical Excellence (NICE) guidance 'risk identification and intervention for individuals at high risk of diabetes' (NICE 2012).

Chapter Eight reports the STAND randomised controlled trial, designed to assess whether the STAND programme is effective at reducing sedentary time and improving cardio-metabolic health in young adults at risk of T2DM. This chapter focuses on sedentary time, the primary outcome of the trial, in addition to the biomedical data. This chapter is the culmination of the previous chapters and is a central part of this thesis. The findings are likely to have important implications for future research and practice.

Chapter Nine provides a summary of the main findings in this thesis and discusses the overall implications and future research directions of the work presented.

The findings in this thesis have been widely disseminated through publications in peer reviewed journals, presentations at national and international conferences and through media interest in some of the findings. I have also won a number of prizes and awards relating to the work in this thesis. A summary of the conference presentations and the full text of published manuscripts is available in Appendix Six. A list of my prizes and awards is available in Appendix Seven and details of the media interest in my systematic review and meta-analysis, described in Chapter Four, is available in Appendix Eight.

Primary research aims

The primary aims of this thesis are to:

1. Determine the implications of a diagnosis of T2DM in young adults (aged <45 years)
2. Conduct a systematic review and meta-analysis to analyse the association between of sedentary behaviour and diabetes as well as cardiovascular disease, and cardiovascular and all-cause mortality
3. Design and assess a theory driven sedentary behaviour intervention for young adults identified as high risk for the development of T2DM

Chapter Two: Type 2 diabetes in younger adults literature review

Chapter Overview

Chapter Two aims to provide an overview of the epidemiology, aetiology, pathophysiology, diagnosis, complications, co-morbidities and clinical management of Type 2 diabetes (T2DM) in younger adults. This sets the scene for Chapter Three, the Expedition study which aims to phenotype young adults with T2DM, and Chapters Five, Six, Seven and Eight which describe the development and assessment of a lifestyle intervention designed to reduce sedentary time in younger adults at risk of T2DM.

Abstract

There is an emerging epidemic of T2DM in younger adults. They represent an extreme phenotype: likely to be obese, lead a sedentary lifestyle, have a strong family history of T2DM, be from black and minority ethnic (BME) origin and come from less affluent socio-economic groups. An accurate diagnosis of T2DM in younger adults, whilst essential to guide management, can be challenging even for the experienced diabetologist. Co-morbidities such as hypertension, nephropathy and hyperlipidaemia are prevalent in this group, and despite the lack of longitudinal data, they represent a very high risk group, with a need for aggressive management. This focused review of the epidemiology, aetiology, clinical outcomes, co-morbidities and management of younger adults with T2DM will provides the latest insights into the UK's emerging epidemic.

Introduction

Until recently T2DM was considered a disease of older adults but alarmingly we are now seeing the condition diagnosed in children, adolescents and young adults under the age of thirty (Kitagawa et al. 1998, Dabelea et al. 2009, Braun et al. 1996, Drake et al. 2002). While type 1 diabetes (T1DM) remains the main form of diabetes in young people, it is anticipated that T2DM will be the predominant form within 10 years in some ethnic groups (Alberti et al. 2004).

The onset of T2DM in younger adults presents a number of problems for both the individual and society. The youth with T2DM represents an extreme phenotype. They are likely to be obese, have a multigenerational family history of T2DM, lead a sedentary lifestyle, be of black or minority ethnic (BME) origin and come from socially deprived groups (Feltbower et al. 2003, Haines et al. 2007, Millett et al. 2008). From a societal perspective, the explosion of younger adults developing T2DM has huge implications for future workforce and health care systems.

The main objectives of this review are to:

- Describe the epidemiology of T2DM in younger adults, with particular reference to the UK
- Describe the typical phenotype of the younger adult with T2DM: the clinical presentation and diagnostic difficulties
- Outline the complications, co-morbidities and management
- Discuss the impact of T2DM on women of child bearing age.

Definition of Type 2 diabetes in younger adults

T2DM in younger adults has been defined in a variety of ways, often separating the paediatric (<18 years) from the adult (>18 years) population. However, there is a continuum of risk associated with an earlier diagnosis of T2DM and this distinction may fail to recognise the potential for poorer outcomes in patients diagnosed in their third and fourth decades of life. For the purpose of this review, T2DM in younger adults will include the high risk cohort up to and including the age of 45 years. This cut off has been selected for two reasons: firstly, there is a 4 fold increase in the risk of myocardial infarction for those diagnosed with T2DM <45 years compared to those aged >45 years (Hillier et al. 2003); secondly the cut off of <45 years will include women of child bearing age, a cohort which requires special consideration.

Epidemiology

Most of the evidence for an epidemic of T2DM in younger adults has come from paediatric data from Japan and the USA. Between 1990 and 2000 New York experienced a 10 fold increase in the prevalence of T2DM in children (Grinstein et al. 2003). The SEARCH for diabetes in youth study in America has reported incidence and prevalence rates of 3.7-19/100,000 per year and 0.18-1.06/1,000 respectively, with higher rates seen in black and minority ethnic groups (Dabelea et al. 2009, Bell et al. 2009, Mayer-Davis et al. 2009, Lawrence et al. 2009, Liu et al. 2009). Japan has also experienced a doubling in the incidence of T2DM in children between the late 80s and early 1990s and T2DM is now the most likely diagnosis in a child presenting with diabetes in this country (Kitagawa et al. 1998). T2DM in younger adults has also been reported in China, Mexico, India and Australia (Braun et al.

1996, Dabelea et al. 1998, Gu et al. 2003, Ramachandran et al. 2003). However, reports in the Europe are rarer. A European survey and literature review in 2005 discovered only 184 children and adolescents with T2DM of which the majority were Caucasian and female with a positive family history of T2DM (Malecka-Tendera et al. 2003). A more recent population wide study in Germany identified 562 children with T2DM, representing 1.4% of the diabetic population under the age of 20 years (Schober et al. 2009).

Most UK data on the incidence and prevalence of T2DM in younger adults has been reliant on reports from secondary care paediatric units. A cross-sectional questionnaire survey of all UK paediatric centres in 2000 identified 25 patients under the age of 16 years with T2DM, with a crude prevalence of 0.21/100,000 (Ehtisham et al. 2004). A prospective monthly surveillance of UK paediatricians between 2004-2005 estimated the incidence of T2DM in those <17 years to be 0.6/100,000 per year, much lower than the SEARCH for diabetes in youth figures (Haines et al. 2007, Shield et al. 2009). However, UK surveys have been reliant on doctors and nurses reporting data to a central surveillance unit and are therefore likely to underestimate the true incidence of T2DM in this age group within the UK.

Some of the UK population data on the prevalence of T2DM in children and adolescents is derived from general practice prescriptions of oral anti-diabetic therapies. This recently published retrospective cohort study analysed prescriptions issued between 1998 and 2005 for 505,754 young adults aged <18 years. During this period there was an eightfold increase in prescriptions for oral anti-diabetic therapy (Hsia et al. 2009). The prevalence of T2DM in this study was estimated at

1.9/100,000, almost 10 times higher than the original report in 2000 of 0.21/100,000. This probably reflects the limitations of the previous questionnaire based surveys and the fact that the paediatric surveillance surveys gathered data on those up to the age of 16 whereas the GP prescription data base looked at children up to 18 years of age. Nonetheless, these data are striking, indicating a significant rise in the incidence and prevalence of T2DM in youth in the UK.

The most recent data on T2DM in younger adults is from a national survey of England in 2009. This identified 328 youth with T2DM under age 18, representing 1.5% of the total diabetic population in this age group. The estimated prevalence was 3.0/100,000 with peak prevalence in 10-14 year olds (Mayor et al. 2010). This report adds further support to the hypothesis that we are seeing a rapid rise in the prevalence of T2DM in younger people in the UK (Table 2.1).

Table 2.1. UK studies examining the prevalence of T2DM in children and adolescents.

Study	Year data gathered	Methodology	Estimated prevalence of T2DM
Ethisham, 2004	2000	Cross sectional questionnaire of paediatricians. Included T2DM <16 years.	0.21/100,000
Hsia, 2009	2005	Retrospective cohort study. Analysed oral anti-diabetic prescriptions for children <18 years.	1.9/100,000
Royal College of Paediatrics and Child Health, 2009	2009	Cross sectional survey of secondary care clinicians in England. T2DM <18 years.	3/100,000

Many publications have focused on the paediatric population. However there are some data available from adult diabetes services. A hospital based cross sectional study in Leeds in 2003 described a crude prevalence of 0.13/1000, representing 5% of their diabetes clinic population under the age of 30 years with T2DM (Feltbower et al. 2003). A later report from the same area described a substantial increase in the proportion of their diabetes population aged <29 years with T2DM (12% in 2006) (Harron et al. 2011). A further study in Sheffield in 2008 identified 527 people with T2DM diagnosed before the age of 40 years, representing 24% of their total clinic population (Song et al. 2009). Data from a retrospective review of our secondary care diabetes service in Leicestershire identified 185 people with T2DM under the age of 35 years, representing 14% of the diabetes clinic population (Benhalima et al. 2011). These data suggest that T2DM diagnosed in younger adults represents a substantial proportion of patients utilising secondary care services. Although there is increasing evidence for a rise in the incidence and prevalence of T2DM in younger adults in the UK, more robust epidemiological data is required to describe this population and the associated natural history and clinical outcomes.

Screening for T2DM in younger adults

People with T2DM in the early stages have little or no symptoms and can go undiagnosed for many years. The early detection and management of T2DM has the potential to limit the impact of the disease. Population screening for T2DM in older adults has led to yields of up to 6% (Mostafa et al. 2010, Greaves et al 2004). Unfortunately similar data do not exist for younger adults. The National Institute of Clinical Excellence has recently recommended screening for T2DM in young adults aged 25-39 years who are from black or minority ethnic groups or who have

conditions which increase their risk of T2DM. However, data on the effectiveness of this approach in terms of T2DM yield and long term outcomes is currently lacking (NICE, 2012, Deakin 2012).

Risk factors

The risk factors for T2DM in youth are similar to those for late onset T2DM, with the additional risk factors of puberty contributing to insulin resistance. Furthermore, in contrast to late onset T2DM diabetes, T2DM in youth is more common in females (Table 2.2).

Table 2.2: Risk Factors for T2DM in youth

Modifiable	Non-modifiable
Obesity Low physical activity High sedentary behaviour Socioeconomic status	Ethnicity (Pima Indians, Hispanics, Asians and Afro-Caribbeans) Family history T2DM Puberty Low birth weight Exposure to DM in the uterus Female sex Previous gestational diabetes

Obesity

Obesity is one of the key factors driving increasing rates of T2DM in younger people. Obesity is the outcome of a positive energy balance, often the result of the combination of excess dietary intake and a sedentary lifestyle. Overall, 80-92% of young adults diagnosed with T2DM in the UK are obese compared with only 56% of adults (Shield et al. 2009, Hsia et al 2009, Gonzalez et al. 2009). This data is in keeping with international findings (Liu et al. 2020). Data from America demonstrate an inverse linear relationship between body mass index (BMI) and the age at diagnosis of T2DM (Hillier et al. 2001). An age at diagnosis of <30, 51-55 and >70

years was associated with a BMI of 38.3, 35.0 and 28.8 kg/m² respectively (Hillier et al. 2001). These data support the hypothesis that T2DM in younger adults is driven by increasing levels of obesity.

Low physical activity and high sedentary time

Physical inactivity is one of the key factors in the obesity and diabetes epidemic in younger people. The European Youth Heart Study found that clustered metabolic risk (including insulin sensitivity) increased in a dose response manner with decreasing MVPA in children aged 9-15 years (Ekelund et al. 2007, Andersen et al. 2006). Longitudinal data from the USA has clearly demonstrated that the steep decline in MVPA in adolescence is associated with increased weight gain (Kimm et al. 2005). This is concerning given recent accelerometer data from the UK has highlighted that only 7% of boys and 0% of girls aged 11-15 years met the government recommendations of 60 minutes of MVPA per day (Rodriguez-Moran et al. 2006).

In addition to failing to meet the recommend physical activity guidance, with the increasing use of computers and television in leisure time, there is mounting concern about the amount of time younger people spend sedentary (sitting). Excess sedentary time has been associated with dysglycaemia, T2DM, cardiovascular disease and mortality (Dunstan et al. 2012, Hu et al. 2003, Katzmaryzk et al. 2009). However, intervention studies to assess the impact of reducing sitting time on health in young people have not yet been performed. Sedentary behaviour is ubiquitous and is a potentially modifiable risk factor for T2DM in young people.

Family History

Family history of diabetes and genetic predisposition undoubtedly play a significant role in the development of T2DM in youth. In the UK 84% of adolescents with T2DM have a family history of T2DM and 56-71% have a parent or sibling affected (Haines et al. 2007, Shield et al. 2009). Both genetic and environmental factors will have a role to play. Although there is clear evidence of a genetic predisposition to insulin resistance, families often share a similar environment (Rodriguez-Moran et al. 2006).

Ethnicity

Internationally, Japanese, Hispanics and Native Americans have the highest risks of developing T2DM in childhood (Dabelea et al. 2009, Lawrence et al. 2009, Liu et al. 2009, Chan et al 1993). In the UK 43-56% are from a Black or Minority Ethnic origin with prevalence rates of 3.9/100,000 in Black, 1.25/100,000 in South Asians compared to the much lower rate of 0.35/100,000 in White children (Haines et al. 2007).

Clinical presentation and diagnostic criteria

The younger person with T2DM is often obese, from a BME background and has a family history of diabetes. However, with increasing rates of obesity in the general UK population, making a diagnosis of T2DM is not as straightforward as it might first appear. Getting the diagnosis correct is crucial – misdiagnosing a patient with T2DM when they actually have T1DM could be life threatening if the choice of management is metformin and not insulin, a life saving treatment in T1DM. Labelling a patient with T1DM when they actually have T2DM could be similarly disastrous as the patient may be subjected to lifelong unnecessary treatment with insulin instead of being

given the option of oral therapies, or some of the newer weight loss inducing incretin mimetic therapies. Misclassification may also result in negative psychological effects in both the individual and their family (Stone et al. 2010). Even if the misclassification is corrected, such effects may persist, for example, annoyance and a lack of confidence in the doctor for both inappropriate labelling and the resultant sub-optimal management (Shepherd et al. 2004).

It is therefore essential that patients are correctly classified at diagnosis. T2DM occurs when insulin secretion is inadequate to meet the increase demand posed by insulin resistance and as such other features of insulin resistance are often present in patients with T2DM: hypertension, hyperlipidaemia, acanthosis nigricans (a cutaneous manifestation of insulin resistance), polycystic ovarian syndrome and non-alcoholic fatty liver disease.

In addition to the clinical features, the clinical presentation can help to guide the physician. T1DM often has a rapid onset with a few weeks history of polyuria, polydipsia and weight loss and at presentation most of these patients have decompensation in the form of ketosis or diabetic ketoacidosis. In contrast the patient with T2DM presents insidiously – many are diagnosed as an incidental finding or some may present with osmotic symptoms. However, confusion can arise because up to a third of patients with T2DM can present with ketosis or ketoacidosis, which can result in misclassification as T1DM (Rosenbloom et al. 2003).

Ketosis prone T2DM describes a group of patients who present with ketosis or ketoacidosis who then enter a period of near normo-glycaemia remission. Ketosis

prone T2DM can affect up to 50% of African American and Hispanic patients presenting with diabetic ketoacidosis (Maldonado et al. 2005, Maldonado et al. 2004). These individuals have the typical phenotype of T2DM in youth: usually obese, with a strong family history of diabetes. At diagnosis they have severe impairment of their insulin secretion. This improves with insulin therapy, often allowing the discontinuation of insulin after a few months of treatment. This unexplained effect is thought to result from the “glucotoxic” effects of hyperglycaemia on the beta cells in the pancreas (Umpierrez et al. 1995, Mauvais-Jarvis et al. 2004). When in remission, these patients can be managed on low dose sulphonylurea or metformin: diet alone has been shown to shorten the remission period (Umpierrez et al. 1995, Umpierrez et al, 1997).

Monogenic diabetes, formerly known as Maturity Onset Diabetes in the Young (MODY), is a diagnosis which should be considered in younger patients presenting with atypical diabetes. At the turn of the century monogenic diabetes was more common than T2DM in children although more recent European reports would suggest that this is no longer the case (Schober et al. 2009, Ehtisham et al. 2004). Monogenic diabetes is an inherited condition arising from a mutation in a single gene which regulates beta cell function. Previous classification of MODY included a diagnosis of diabetes <25 years, autosomal dominant inheritance and non-insulin dependence (Ehtisham et al. 2000, Ehtisham et al. 2004). However, many younger patients with T2DM also meet these criteria and as such the classification has subsequently been revised (Hattersley et al. 2009). A diagnosis of monogenic diabetes should be considered when the patient is not markedly obese, is from an ethnic background with a low prevalence of T2DM (e.g. Caucasian) and has no

evidence of insulin resistance (a fasting c-peptide in the normal range and no acanthosis nigricans) (Hattersley et al. 2009). If suspected, monogenic diabetes should be confirmed with molecular genetic testing, especially in cases where a diagnosis of monogenic diabetes could alter the clinical management (for instance in the case of HNF1 α , patients are sulphonylurea sensitive allowing discontinuation of insulin therapy). Further information can be obtained from the ISPAD clinical consensus guidelines (Hattersley et al. 2009). Table 2.3 lists some of the main distinguishing features of T1DM, T2DM and Monogenic diabetes.

A further consideration in making a diagnosis of T2DM in a young person is the role of auto-antibodies such as glutamic acid decarboxylase, islet cell or insulin autoantibody. Previous studies have used the presence or absence of auto-antibodies to classify patients with T1DM or T2DM respectively (Haines et al. 2007). However, the recent International Society for Paediatric and Adolescent Diabetes clinical practice consensus guidelines have identified “autoimmune T2DM” as a classification in light of the fact that 15-40% of youth and adults with T2DM have T1DM associated antibodies, including those not requiring insulin one year after diagnosis (Rosenbloom et al. 2009). However, these individuals have significantly impaired insulin secretion and many require insulin treatment at an earlier stage (Tfayli et al. 2009). Therefore auto-antibodies cannot be viewed as a diagnostic tool, as some patients with T2DM will be anti-body positive, but they may guide clinical management. As such, current guidelines recommend these are measured at the time of diagnosis in all young people presenting with diabetes (Rosenbloom et al. 2009).

Laboratory measures which further aid the classification of diabetes subtype include insulin and C-peptide values. A high serum C-peptide is indicative of endogenous insulin secretion and a persistently elevated value would be unusual in T1DM (Rosenbloom et al. 2009). However there is substantial overlap in insulin and C-peptide values between T1DM and T2DM at diagnosis, so these laboratory tests are often not useful until the patient has had diabetes for several years. The recent development of a post-meal urine C-peptide/creatinine ratio may allow for an inexpensive and practical differentiation between diabetes subtype. Preliminary data have suggested that this non-invasive, home-based test can reliably distinguish between T1DM and T2DM (Besser et al. 2010).

Diagnosing a young person with T2DM can be difficult. There is no clear cut definition and the diagnosis is often a balance of probability and minimization of risk to the patient. It can often take months or years to ascertain diabetes classification and a label of “Diabetes – cause uncertain” is entirely appropriate during this time (De Lusignan et al. 2010). If there is any doubt over the classification at diagnosis and the patient is symptomatic it is safest to treat with insulin to prevent decompensation. Given the complexity associated with such cases I would advocate specialist input and management, at least initially, of any young person presenting with new onset diabetes.

Table 2.3: Features which help differentiate between T1DM, T2DM and monogenic diabetes. Adapted from Alberti et al (2004) and Craig et al (2009).

	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes
Frequency	>90%	<10% depending on country (Japan 60-80%)	1-3%
Clinical picture	Onset acute—symptomatic with weight loss, polyuria and polydipsia	Slow—often asymptomatic	Variable, can be incidental finding
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Parent with diabetes	2-4%	80%	90%
Ketosis	Almost always present	Usually absent	Common in neonatal forms, rare in others
C-peptide	C-peptide negative	C-peptide positive	C-peptide normal range
C-peptide/creatinine ratio	Low	High	Normal
Antibodies	ICA positive Anti-GAD positive ICA 512 positive	Negative	Negative
Therapy	Insulin invariably	Oral hypoglycaemic agents	Variable ranging from diet, to sulphonylurea to insulin therapy depending on sub-type
Associated autoimmune diseases	Yes	No	No

Clinical outcomes

Microvascular complications

Nephropathy

A high proportion of children and adolescents with T2DM have microalbuminuria with prevalence estimates of 7-22% at diagnosis, 28-42% 5 years after diagnosis and 60% 10 years after diagnosis (Eppens et al. 2006). Younger adults with T2DM aged <18 years have higher rates of microalbuminuria (28 vs 6%) and hypertension (36 vs 16%) compared to people with T1DM, despite a shorter duration of diabetes (1.3 years vs 6.8 yrs) and lower HbA1c (7.3% vs 8.5%) (Eppens et al. 2006). Pima Indians, diagnosed with T2DM <20 years, have been shown to have a five fold increase in the risk of the development of end stage renal failure in middle age compared with T1DM while Japanese data report a significantly higher cumulative incidence of nephropathy in younger adults diagnosed with T2DM under the age of 30 years compared with T1DM (44 vs 20%, $p<0.0001$) (Pavkov et al. 2006, Yokoyama et al. 2000). A large Canadian dataset has more recently reported a four-fold increased risk of renal failure compared to T1DM counterparts and a 23-fold increase compared to control subjects (Dart et al. 2012). Kaplan Meier 10 year renal survival was 100% at 10 years for both the T1DM and T2DM groups. However, survival fell to 92% at 15 years and 55% at 20 years in the T2DM group but remained stable in the T1DM group (Dart et al. 2012). These data suggest that there are inherent differences in the renal risk between T2DM and T1DM in youth. Interestingly, systolic hypertension was not a risk factor in the Dart et al cohort while renin angiotensin aldosterone system (RAAS) pathway inhibition was (15.8 fold increased risk of renal failure). While this may reflect confounding from disease

severity, it is important to reflect on the fact that, despite the benefits seen in the older population with T2DM, we do not yet have evidence of benefit from RAAS blockade in the younger population.

Neuropathy

Comparing a sample of UK adolescents with T2DM (n=7) and T1DM (n=120), 57% of those with T2DM had evidence of peripheral neuropathy when assessed using light touch/ vibration sense whereas none of those with T1DM had evidence of peripheral neuropathy (Karabouta et al. 2008). In another UK study, 12 of 30 (40%) patients aged 13-35 years had evidence of neuropathy, 6 (20%) of whom had evidence of ulceration (Paisey et al. 2009). This would suggest that neuropathy can present in younger adults with T2DM at an earlier stage (mean duration of diabetes was 1.8 years).

Retinopathy

Limited data is available on retinopathy in T2DM younger adults, especially from the UK. Overall, studies suggest that retinopathy is rare in T2DM compared with T1DM in younger adults, although these figures fail to account for the dramatically shorter duration of diabetes in T2DM (Shield et al. 2009, Eppens et al, 2006). A population based cohort study in Sweden found similar rates of retinopathy between groups but the incidence of severe retinopathy was significantly higher in younger adults aged 15-34 years with T2DM compared with T1DM both at diagnosis and follow-up 10 years on (Henricsson et al. 2003). In a survey of UK children with T2DM no retinopathy was reported but this is likely to be an underestimate given 22% of this population were not screened (Shield et al. 2009). A detailed retinal assessment of a

small number of adolescents with T1DM and T2DM versus healthy controls has identified subclinical structural and functional retinal abnormalities which were more pronounced in the T2DM group compared with the T1DM group (Bronson-Castain et al. 2012). This was despite a shorter duration of T2DM (2.1 vs. 5.7 years).

Macrovascular risk factors and complications

Lipids

Dyslipidaemia is very common with elevated cholesterol and triglyceride values in 33-60% of younger adults aged <18 years with T2DM (Bell et al. 2009, Eppens et al. 2006, Zdravkovic et al. 2004, Upchurch et al. 2003). These rates are higher than rates found in non-diabetic obese counterparts suggesting that the diagnosis of diabetes has an additive impact on dyslipidaemia.

Hypertension

30-55% of adolescents with T2DM are hypertensive at presentation (Eppens et al. 2006, Zdravkovic et al. 2004, Upchurch et al. 2003). From UK paediatric data only 1 in 5 patients aged <17 years had a recorded blood pressure measurement. 34% were hypertensive, although none were on treatment (Shield et al. 2009).

Surrogate markers of cardiovascular disease

T2DM in younger adults is still a relatively recent phenomenon and given the paucity of data on cardiovascular outcomes, we are currently reliant on surrogate markers of heightened cardiovascular risk. Aortic pulse wave velocity, a predictor of cardiovascular mortality in adults, is significantly higher in adolescents with T2DM

compared to age matched obese and T1DM controls (Gungor et al, 2005, Wadwa et al 2010). Vascular stiffness was comparable to adults aged >40 years (Gungor et al. 2005). Significant abnormalities in carotid structure and function have also been demonstrated in young adults with T2DM aged 10-24 years, with significantly greater carotid intima-media thickness than lean and obese participants (Urbina et al. 2009, Naylor 2011). These data provide support for the assumption that T2DM in younger adults will be associated with poor cardiovascular outcomes in the future.

Cardiovascular morbidity and mortality

There are only very limited follow-up data from T2DM in younger adults and to date we are unable to adequately describe cardiovascular outcomes in this rapidly expanding group. A modelling study has recently estimated that the diagnosis of T2DM in ages 15-24 years will be associated with a 15 year reduction in life expectancy and, for some, the development of severe chronic complications in their 5th decade (Rhodes et al. 2012). Preliminary data from 69 First Nation Canadians adolescents with T2DM, followed up for 9 years, showed that the mortality rate during this period was 9%. Of the remaining survivors, 35% developed microalbuminuria, 45% were hypertensive and 6% were on dialysis (Dean et al. 2002). However, these patients were cared for in a pre-UKPDS/pre-DCCT era and their glycaemic control was extremely poor with a mean HbA1c of 10.9%. There is further evidence available from America which supports the hypothesis that outcomes in young onset T2DM will be worse than in late onset. For instance, the hazard of developing a myocardial infarct in early-onset T2DM (<45 years) is 4-fold higher than in late onset T2DM (>45 years) and 14-fold higher than in people without diabetes (Hillier et al. 2003). This evidence for increased cardiovascular morbidity in

those diagnosed with T2DM at a younger age is further supported by a large prospective cohort study of 4857 American Indian children who were followed up for 24 years. In this study obesity, glucose intolerance and hypertension increased the risk of premature death by 130%, 73% and 57% respectively (Franks et al. 2010). Although these studies did not examine the impact of T2DM per se, they provide some insight into the potentially devastating impact T2DM in younger adults may have in the future.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver abnormality seen in children and is present in approximately 50% of children with T2DM (Bloomgarden et al. 2007, Schwimmer et al. 2008). There is a spectrum of NAFLD ranging from infiltration (steatosis) to inflammation (steatohepatitis) to liver cirrhosis. It is commonly associated with insulin resistance. A “multi-hit” hypothesis has been proposed to describe the pathogenesis of NAFLD (Day et al. 1998, Jou et al. 2008). Insulin resistance and the associated increase in free fatty acids which are absorbed by the liver represent the first “hit” and the development of steatosis. The second “hits” involve the complex interactions between hepatocytes, adipose cells and inflammatory biomarkers which result in inflammation or cirrhosis (Jou et al. 2008).

Affected individuals are often asymptomatic and the most common manifestation of this condition is an elevated ALT level, typically higher than the AST level. Of those with NAFLD, 30% of affected individuals will have fatigue, 30% will have right upper quadrant abdominal pain and 25% will have enlargement of the liver on ultrasound (Bloomgarden et al. 2007). Many children with NAFLD will go on to develop liver

fibrosis or cirrhosis with 3-10% already having cirrhosis at the time of liver biopsy. A 20 year follow-up study of adolescents with NAFLD (without diabetes) reported that 6% died or required a liver transplant with a standardised morality ratio of 13.6 (Feldstein et al. 2009). This would suggest that the combination of T2DM *and* NAFLD developing early in life is likely to lead to substantial morbidity and mortality.

There is an urgent need for effective therapies to prevent progression to liver fibrosis. The insulin sensitising glitazones improve steatosis and inflammation in NAFLD, raising the question of whether these agents should be prioritised for use in patients with T2DM with NAFLD (Belfort et al. 2006, Ratziu et al, 2008). However, there is no robust evidence for a reduction in liver fibrosis and side effects include persistent weight gain, oedema and an increased fracture risk (Kahn et al. 2006, Sanyal et al. 2010, Ratziu et al. 2010). Although the effect on histology is unclear, diet, exercise and metformin have all been associated with improvements in liver function tests and inflammation and as such the authors would advocate these treatments as first line therapies in the younger adults with T2DM and NAFLD (Marchesini et al. 2004, Nair et al, 2004, Ueno et al, 2007, St George et al. 2009).

T2DM and Pregnancy

There has been a substantial increase in the number of women with T2DM attending maternity services. A third of the women in the UK Confidential Enquiry into Maternal and Child Health (CEMACH) report had T2DM (CEMACH 2007). T2DM in pregnancy is associated with a number of risks for both the mother and fetus, with outcomes for women with T2DM are just as poor as for women with T1DM. These include miscarriage, preterm labour, macrosomia, birth injury, neonatal hypoglycaemia and

stillbirth in addition to a two fold increase in the rate of congenital malformations and a threefold increase in the risk of perinatal mortality (CEMACH 2007).

The risks associated with diabetes and pregnancy can be minimised through meticulous glycaemic control (HbA1c <6.1%), high dose folic acid (5mg a day) combined with close monitoring of the mother and fetus (NICE 2008). Unfortunately women with T2DM are less likely to have pre-pregnancy counselling, preconception folic acid or a test of glycaemic control in the 6 months before conception when compared to women with T1DM (CEMACH 2007).

As highlighted in the complications section, young women with T2DM often have other co-morbidities (obesity, hypertension, microalbuminuria etc.) in addition to diabetes which further increase the risks in pregnancy. Despite the equal prevalence of co-morbidities in males and females, there seems to be a reluctance to treat women of child bearing age as aggressively as men. An audit of our local population with T2DM <35 years revealed that fewer women were treated for hypertension (22% vs. 43%, $p<0.01$) and hypercholesterolaemia (16% vs. 43%, $P<0.01$) than men, despite similar rates of hypercholesterolaemia and hypertension (Benhalima et al. 2010).

Nonetheless, UK data from our group demonstrates a rapid increase in the use of potentially teratogenic anti-hypertensive and statin therapies in young women with T2DM over 10 years, with no concomitant increase in the use of contraception (Webster et al. 2010, Makda et al. 2012). This is a reflection of the fact that only 1 in 10 women has a documented discussion about the risks of diabetes and pregnancy

while only 4 in 10 are given advice on contraception (CEMACH 2007). There is need for national guidance on contraception in women with T2DM to facilitate the aggressive management of cardiovascular risk out with pregnancy.

Management

Currently, metformin and insulin are the only drugs approved for use in the paediatric population with T2DM. Metformin inhibits gluconeogenesis and promotes peripheral glucose uptake, improving glucose sensitivity. Few trials have assessed traditional oral hypoglycaemic agents in young people with T2DM. In 2002 a multi-centre double blind trial concluded that metformin was safe to use in 82 subjects aged 10-16 years for up to 16 weeks. This period was associated with a reduction in HbA1c of 1.2% and a 3.6mmol/l reduction in fasting glucose compared to the placebo arm (Jones et al. 2002). Glimepiride, a sulphonylurea, promotes insulin secretion. In 2007 a single blind multi-national study reported that glimepiride reduced HbA1c similarly to metformin in 263 young people with T2DM (mean age 13.8 years). However, the use of glimepiride was associated with a 1.97kg weight gain, compared to only 0.55kg in the metformin group. Safety profiles of both drugs were comparable over the 26-week follow-up period (Gottschalk et al, 2007). The TODAY trial follows on from these preliminary trials and is the largest therapeutic trial to be conducted in a large cohort of youth with T2DM (TODAY study group 2012). In this 4 year follow-up randomised controlled trial, recently diagnosed youth with T2DM were randomly assigned to either metformin alone, metformin and a lifestyle intervention or metformin plus rosiglitazone. The addition of rosiglitazone but not the lifestyle intervention was superior to metformin alone (TODAY study group 2012).. The metformin treatment failure rate was higher than is seen in older adults with T2DM

and suggests that younger adults with T2DM are likely to require more aggressive polypharmacy early in the course of their disease (TODAY study group 2012). Furthermore the benefits of lifestyle interventions in youth with T2DM may be limited but this requires more detailed exploration.

Older adolescents and those over 20 years have access to the full range of anti-diabetic therapeutic options including gliptins and GLP-1 analogues. GLP-1 is released upon ingestion of food, resulting in improved insulin secretion, delayed gastric emptying and the promotion of satiety. Recent advances in the management of T2DM in adults include GLP-1 analogues such as exenatide and liraglutide. The main advantage of these agents over other existing therapies is the combination of improvement in glycaemic control with significant weight loss, the elusive goal in T2DM therapy (De Block et al. 2009). Such agents would, in theory, benefit the younger T2DM population, who tend to have a higher BMI at diagnosis than older adults, but to date clinical trials to assess outcomes in this younger target population have not been performed.

In terms of cardiovascular risk management, lifestyle interventions to reduce weight and increase MVPA are advocated. If, following such changes, younger adults with T2DM have persistent hyperlipidaemia or hypertension, a statin or angiotensin converting enzyme inhibitor should be initiated (Rosenbloom et al, 2009). However, to date there have been no pharmacotherapeutic outcome studies of management of hypertension or dyslipidaemia in younger adults with T2DM.

Conclusion

There is an urgent need to develop a full understanding of the natural history of T2DM in younger adults which include determining population based prevalence rates and the natural history of co-morbidities and complications. As demonstrated, this data is particularly lacking in Europe. The true extent of the morbidity and mortality associated with T2DM in younger adults will not be fully realised for another 10-20 years in Westernised society. It is therefore imperative that effective primary and secondary prevention strategies are rapidly developed to prevent the growing burden of T2DM on the individual, society, health care systems and work forces throughout the developed world.

Chapter Three: The Expedition Study to phenotype young adults with Type 2 diabetes

Chapter Overview

Chapter Three builds on Chapter Two by providing a more detailed insight into the effects of an early diagnosis of T2DM in younger adults. In this chapter I report the methods and results for the Expedition study (Early Detection of Cardiac Dysfunction and Health Behaviours in the Young with Type 2 Diabetes Mellitus), a Medical Research Council funded study to phenotype a cohort of young adults with T2DM. I was responsible for developing the study documents, submitting the study for regional Research Ethics Committee and local Research and Development approval. I managed the study throughout and was personally responsible for participant recruitment, consent and data collection. I attended and oversaw all study visits. However, this study was a multidisciplinary study and a team of cardiologists, led by Dr Gerry McCann, conducted and analysed the cardiac magnetic resonance (CMR) data (I observed every CMR and interpreted the data obtained). Similarly, Dr Melanie Leggate, an exercise physiologist, led the VO₂ max tests and performed the inflammatory biomarker laboratory analysis (I supervised all VO₂ max tests and took the blood samples for the inflammatory biomarkers).

Abstract

Aim: To phenotype young adults with T2DM.

Methods: 20 T2DM patients (aged 18-40 years), 10 lean (LC) and 10 obese (OC) controls underwent detailed assessment, including cardiac magnetic resonance (CMR) imaging, inflammatory proteins, lipids, vitamin D, VO_{2max} and habitual physical activity. Outcomes were compared between T2DM and control groups.

Results: Mean (SD) age, T2DM duration and BMI in the T2DM group were 31.8 (6.6) years, 4.7 (4.0) years and 33.9 (5.8) kg/m² respectively. Compared to LC, those with T2DM had more deleterious profiles of hyperlipidaemia, vitamin D deficiency, inflammation, physical activity and VO_{2max} . However, there was no difference between T2DM and OC groups. The T2DM group had preserved systolic cardiac function but higher left ventricular mass than the LC ($p=0.002$) but not the OC ($p=0.60$). There was a strong trend towards progressively reduced global peak systolic strain from LC (-23.48 (2.86)%) to OC (-23.30 (2.62)%) to T2DM (-21.20 (2.75)%, $p=0.08$ v LC, $p=0.08$ v OC). Peak early diastolic strain rate was reduced in T2DM (1.51 (0.24)/s) compared with LC (1.97 (0.34)/s, $p=0.001$) and OC (1.78 (0.39)/s, $p=0.042$).

Conclusion: Young adults with T2DM are characterised by an adverse cardiovascular risk profile, with evidence of increased left ventricular mass and subclinical diastolic dysfunction. These findings are concerning and suggest an increased risk of future heart failure and mortality.

Introduction

T2DM has previously been perceived as a disease of older adults, however the obesity epidemic is driving an exponential rise in the prevalence of T2DM in younger adults (<40 years). This phenomenon has been reported internationally, including the USA, Japan and the UK (Dabelea et al. 2009, Kitagawa et al. 1998, Hsia et al. 2009). At present, the long-term implications of early-onset T2DM are unknown, but preliminary data suggest that T2DM in younger adults and adolescents is an aggressive form of the disease, with evidence of early kidney, liver, nerve and brain dysfunction (Yau et al. 2010, Dart et al. 2012, Paisey et al. 2009). Many of these complications occur despite a short duration of diabetes and relatively good glycaemic control, leading some to propose that health outcomes will be worse than those seen in type 1 diabetes (Eppens et al. 2006).

Cardiovascular disease risk in young adults with T2DM is unknown but is likely to be underestimated by both risk engines and clinical judgement. A recent modelling study estimated that diagnosis of T2DM in ages 15-24 years would be associated with a 15 year reduction in life expectancy and for some, the development of severe, chronic complications of T2DM in the 5th decade (Rhodes et al. 2012). These findings are unsurprising in view of the co-morbidities associated with the diagnosis of T2DM at a young age, such as non-alcoholic fatty liver disease, hypertension and morbid obesity, all of which are independent predictors of mortality (Feldstein et al. 2009, Sundstrom et al. 2011, Abdullah et al. 2011).

Long-term follow-up data to describe the inevitable morbidity and mortality which will result from the additive effects of early onset T2DM, obesity, and the multiple co-

morbidities that coexist in these individuals are awaited. In the meantime, it is necessary to base treatment decisions on evidence available from surrogate markers of disease progression. The aim of the current study was to extensively phenotype a cohort of younger adults with T2DM (<40 years) to assess the prevalence and severity of clinical and subclinical metabolic and cardiac abnormalities. Additionally we sought to elucidate whether these abnormalities are independently driven by dysglycemia or obesity.

Research design and methods

Twenty young adults with T2DM, aged 18-40 years, were recruited from primary and specialist care services in Leicestershire, UK. I initially wrote a letter of invitation to all patients 18-40 years with T2DM who attended University Hospitals of Leicester. I was unable to recruit sufficient numbers via this route so I submitted a substantial amendment which allowed me to recruit participants via the Primary Care Research Network in Leicester, in addition to offering potential participants £50 as a thank you for their participation in the study. Enrolled participants were classified as having T2DM based on clinical diagnosis, initial diabetes management with diet or oral hypoglycaemic agent therapy and the absence of ketosis. Ten lean (LC) and ten obese (OC) non-diabetic control participants were also recruited. Exclusion criteria were a body weight >150 kg or standard contraindications for cardiac magnetic resonance imaging (CMR). The study was granted approval by the local Research Ethics Committee. I obtained informed verbal and written consent from all participants.

Visit one

Anthropometric and $\text{VO}_{2\text{max}}$ measurements

At visit one I interviewed the participants to ascertain past medical history, drug, family and social history in addition to anthropometric measurements. They also underwent a cardiopulmonary exercise test to determine $\text{VO}_{2\text{max}}$. Arterial blood pressure was measured in the sitting position (Omron, Healthcare, Henfield, UK). Three measurements were obtained and an average of the last two measurements reported. Hypertension was defined as systolic blood pressure $\geq 130\text{mmHg}$ or diastolic blood pressure $\geq 85\text{mmHg}$ or treatment for hypertension (Alberti et al. 2005). Body weight, waist circumference (midpoint between the lower costal margin and iliac crest) and height were measured to the nearest 0.1 kg and 0.1cm respectively. $\text{VO}_{2\text{max}}$ was determined using a continuous incremental exercise test on an electromagnetically-braked cycle ergometer (Lode Excalibur, Groningen, The Netherlands), performed to volitional exhaustion. I provided medical supervision of all $\text{VO}_{2\text{max}}$ tests which were led by Dr Melanie Leggate, an exercise physiologist. Expired air was measured continuously using an on-line breath-by-breath gas analysis system (Ultima CPX, MedGraphics, MN, USA), as well as continuous monitoring of heart rate throughout the test (RS200, Polar Electro, Kempele, Finland). The starting workload and workload increments during the maximal exercise test varied from 25-100 watts depending on how active the individual reported they were during everyday life, with the workload increasing every 2 minutes, by 20-35 W until the end of the test. $\text{VO}_{2\text{max}}$ was identified as the peak oxygen consumption averaged over the highest 30 second period.

Physical activity

Participants were asked to wear a GT3X accelerometer (ActiGraph, Florida, USA) on their waistband (in the right anterior auxiliary line) for 7 consecutive days during waking hours. The accelerometer, which objectively records physical activity in free living conditions, was initialised with a start and stop time and a 15 second epoch. A 'valid day' consisted of at least 10 hours of accelerometer movement data and participants with less than 4 days of valid wear were excluded from the analysis. Non-wear time was defined as 60 minutes of consecutive zeros on all three axes. The duration (minutes/day) spent in sedentary, light, moderate, and vigorous physical activities were defined using standard Freedson (1998) cut-off points (sedentary 0-99, light 100-1951, moderate 1952-5724, vigorous >5724 counts per minute).

Visit two

Approximately 1 week later participants attended fasted, with no exercise, alcohol or caffeine consumption in the preceding 24 hours. I obtained venous access, collected fasting bloods and performed an electrocardiogram. Cardiac magnetic resonance imaging (CMR) was performed under the supervision of Dr Gerry McCann and team.

Cardiac magnetic resonance imaging

This paragraph describes the methods employed by Dr Gerry McCann, senior lecturer in cardiology with a specialist interest in CMR, to conduct and analyse the CMR data. I attended the CMR with the study participants but was not directly involved in the CMR data collection or analysis. Once the analysis of the images was completed, I was responsible for interpreting the overall findings as described later in

this chapter. CMR was performed using a 1.5-T scanner (Siemens, Avanto, Erlangen, Germany). To achieve a high temporal resolution a multiple breath-hold (MBH) scheme was applied, in which data were acquired during brief expiration breath holds, which were interleaved by pauses to inhale and exhale as previously described (Zwanenburg et al. 2005). Three short axis tagged images were planned in mid-systole from the 4 and 3-chamber images at base, mid-ventricular and apical levels. The CMR image assessment was performed offline by the cardiologists who were blinded to patient details. Volumes and mass were determined using QMass software, version 7.1 (Medis, Leiden, the Netherlands). The LV contours were drawn manually and left ventricular end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction (LVEF), and end-diastolic LV Mass (LVM), excluding papillary muscles, were calculated. Values were indexed by body surface area (BSA) denoted by the suffix 'I,' for example, LVMI. LVM was also indexed to height^{1.7} which has been shown to be the best measure to detect left ventricular hypertrophy in taller and obese subjects (Chirinos et al. 2010). Tagging analysis: circumferential strain and strain rates were measured using dedicated software (inTag, v1.0, CREATIS, Lyon, France run as a plug-in for OsiriX Imaging Software v3.8, Pixmeo, Switzerland). Strain and strain rates were calculated as an average of the values obtained at basal, mid-cavity and apical short axis slices to give global measures of peak systolic strain (PSS), peak systolic strain rate (PSSR) and peak early diastolic strain rate (PEDSR) (see Figure 3.1).

Laboratory analysis

Fasting plasma glucose, lipid profile (total cholesterol, HDL, triglycerides) and liver function tests were all measured using standard enzymatic endpoint methods on an

ADVIA Chemistry System (Bayer Healthcare, NY, USA), and the LDL fraction subsequently calculated by the Friedewald formula (1972). Dyslipidaemia was defined as prescribed lipid lowering treatment or triglycerides ≥ 1.7 mmol/l or HDL < 1.03 (males), < 1.29 mmol/l (females) (Alberti et al. 2005). An abnormal alanine aminotransferase (ALT) was defined as > 53 iU/L. HbA1c was measured by ion exchange liquid chromatography (G7; Tosoh, Tokyo, Japan). Vitamin D (25-Hydroxyvitamin D) was quantified using liquid chromatography mass spectrometry (6410 Triple Quad, Agilent Technologies UK Ltd, Wokingham, UK) and deficiency was defined as < 30 nmol/l. Plasma interleukin-6 (IL-6) and c-reactive protein (CRP) were determined via non-commercial sandwich enzyme-linked immunosorbent assays (ELISA) as described previously (Leggate et al. 2010, Gray et al. 2008, Pawluczyk et al. 2011). Commercially available ELISA kits were used to determine plasma adiponectin, tumour necrosis factor- α (TNF- α) and interleukin-10 (IL-10) (R&D systems, Minneapolis, MN), as well as plasma insulin and C-peptide concentration (Mercodia, Uppsala, Sweden). All intra-assay coefficients of variance were below 10%. Routine biomedical results were communicated in writing to both the participant and their general practitioner (see Appendix Two).

Statistical analysis

Participant characteristics were summarised by group (T2DM, LC and OC) with normally distributed data expressed as mean (standard deviation (SD)), non-normally distributed data as median (25th and 75th interquartile range (IQR)), and categorical data as percentage. Normality was assessed using the Kolmogorov-Smirnov test, histograms and normal Q-Q plot. Characteristics in the T2DM group were compared with the LC and OC groups separately. A t-test was used to

compare age and Fisher's exact test used to compare sex and ethnicity. All other characteristics were analysed using ANCOVA modelling, with adjustment for sex and ethnicity. Where the characteristic was not normally distributed, a transformation was applied that made the assumption of normally distributed data reasonable. Statistical tests were performed using SPSS 18.0 software (Statistical Package for the Social Sciences, Chicago, IL) and $p < 0.05$ was considered statistically significant (two-sided).

Results

Participant demographics and VO_{2max} data across groups are displayed in Table 3.1. The groups did not differ by age or sex distribution ($p > 0.05$).

T2DM participants

T2DM duration was 4.7 (4.0) years. Nine patients were female (45%) and ten (50%) were of a black or minority ethnic background. Eighteen (90%) had a family history of diabetes, 14 (70%) had a first degree relative with diabetes. The majority ($n=13$, 65%) had an HbA1c $\geq 7\%$. All ($n=20$) had a detectable C-peptide ($>0.2\text{nmol/l}$). Glycaemic management included metformin ($n=16$, 80%), insulin ($n=5$, 25%), sulphonylurea ($n=3$, 15%), glucagon like peptide-1 analogue ($n=3$, 15%), and dipeptidyl peptidase-4 (DPP4) inhibitors ($n=3$, 15%). Six (30%) and seven (35%) were on anti-hypertensive and statin therapy respectively. Depression (based on self-report) ($n=8$, 40%), acanthosis nigricans ($n=5$, 25%) and polycystic ovarian syndrome ($n=4/9$ females, 44%) were prevalent. The mean BMI was in the obese range and 15 (75%) were hypertensive.

Laboratory outcomes

Biochemical variables are displayed in Table 3.2. Eighteen (90%) of the T2DM participants had dyslipidaemia compared to two (20%) of LC ($p<0.01$) and six (60%) of OC ($p=0.14$). Fasting triglycerides were significantly higher in T2DM compared with LC ($p=0.014$), but this was not significantly different compared to OC ($p=0.13$). Seventeen (85%) in the diabetes group were vitamin D deficient, significantly more than in the LC group ($n=3$, 30%, $p<0.001$) but not the OC group ($n=8$, 80%, $p=0.37$). Alanine transaminase (ALT) was significantly higher in the T2DM vs. LC ($p=0.036$) but not OC ($p=0.11$) groups. Plasma adiponectin was significantly lower in the T2DM than LC ($p<0.001$) group, although there was no significant difference between T2DM and OC ($p=0.15$). T2DM participants had significantly elevated plasma IL-6, TNF- α , IL-10 and CRP in comparison to LC ($p<0.05$), but not OC ($p>0.05$).

Cardiac magnetic resonance imaging

LVM was significantly increased in T2DM compared to LC ($p=0.002$), including when indexed by height ($p=0.010$) but not when corrected for BSA ($p=0.348$). LV systolic and diastolic volumes, indexed to body surface area were reduced in the T2DM group compared with the LC but not OC group and there was a borderline significant increase in LVM/volume ratio in the T2DM compared to the LC group ($p=0.05$), but not compared to OC ($p=0.82$). Tagging data were assessed using an average of apical, mid and basal short axis slices where tagging data was complete [$n=29/40$ subjects] and average of the mid and basal slices where tagging data was incomplete [$n=11/40$]. Global systolic function (ejection fraction) was preserved however there was a strong trend towards reduced PSS in the T2DM group compared to both control groups ($p=0.08$ v LC, $p=0.08$ v OC). PSSR was similar

across all groups. PEDSR was significantly reduced in T2DM compared with LC ($p=0.001$) and OC ($p=0.042$), with a progressive decrease in values from LC to OC to T2DM (Table 3.3). Tagged images were not suitable for analysis at the apical level in 8 of the 20 T2DM participants. For completeness, the tagging analysis was repeated in those with complete data sets (apical, mid and basal slices available for analysis, $n=29$, 11 T2DM, 10 LC and 8 OC). The results for PSS and PSSR were essentially unchanged. The progressive decrease in PEDSR values from LC (1.97 (0.34)) to OC (1.87 (0.38)) to T2DM (1.53 (0.23)) persisted, although the difference in PEDSR between the T2DM and the OC groups just failed to reach statistical significance ($p=0.055$).

Cardio respiratory fitness and physical activity

VO_{2max} relative to body mass was lowest in the T2DM group (23 (5) ml/kg/min), followed by OC (25 (7) ml/kg/min, $p=0.26$) and then LC (42 (7) ml/kg/min, $p<0.001$). Criteria for valid accelerometer wear time were met in 16 (80%) of T2DM, all of the OC and nine (90%) of LC participants. Accelerometer data demonstrated that the T2DM group performed significantly less moderate-to-vigorous physical activity (MVPA) than the LC group (33 (28) vs. 54 (19) minutes/day, $p=0.023$) but similar amounts to the OC group (33 (28) vs. 36 (26) minutes/day, $p=0.28$). All groups spent the majority of their time in sedentary behaviours (T2DM 72%, LC 75%, OC 70%) and there were no significant differences between the groups.

Discussion

Despite a young age and relatively short duration of T2DM, the young adults in this study were characterised by dyslipidaemia, hypertension, abnormal liver function,

vitamin D deficiency, low physical fitness and a pro-inflammatory state. Interestingly, apart from parameters of glycaemia and insulin, there was no meaningful difference in many of the measured biochemical variables, including dyslipidaemia, abnormal liver function, markers of chronic low-grade inflammation and vitamin D, between T2DM and OC groups. This suggests that many of these adverse clinical features are driven by obesity, highlighting the need for targeted preventive action in younger adults with obesity. In addition to the biochemical data, structural and functional differences in the heart were detected by CMR in T2DM. Specifically, the T2DM group had higher cardiac mass and lower indexed volumes than the LC group and importantly, diastolic strain rate was significantly reduced in T2DM compared with both LC and OC suggesting that the observed subclinical cardiac dysfunction in T2DM may be additive to the effect of obesity.

The main strength of this study is the detailed and rigorous phenotyping of a multi-ethnic cohort of young adults with T2DM. A further strength of the current study is the inclusion of both obese and lean control groups, which helps elucidate whether obesity or dysglycaemia is the main driver of the abnormalities identified. Another strength is the use of CMR, the gold standard non-invasive technique for the assessment of left ventricular volumes and function. Limitations include the cross-sectional nature of this study that negates the ability to infer causality. In addition, lifetime exposure to obesity and dysglycaemia may have a significant role to play in many of the outcomes measured and our inability to capture this may have contributed to the lack of difference between the obese and T2DM groups for some of the outcomes. The small sample size and the loss of apical tagging data increases

the potential of a type 2 error whereby small, potentially clinically important, differences between the T2DM and OC groups may not have been detected.

The diastolic dysfunction seen in the T2DM group suggests that cardiac dysfunction develops early. Diastolic dysfunction is recognised as the earliest manifestation of diabetic cardiomyopathy, leading to impaired quality of life, reduced exercise tolerance, heart failure and death (von Bibra et al. 2010). Middle-aged adults with T2DM and diastolic dysfunction have a 37% increased risk of developing heart failure within 5 years (Rider et al. 2009). This is the first study to use gold-standard CMR measures of cardiac function and structure in this group of young people with T2DM. The results are consistent with previous echocardiogram studies that have also shown diastolic abnormalities by echocardiography in young people with diabetes compared with lean and obese controls (Shah et al. 2011, Whalley et al. 2009). An area of concern is the loss of data from apical tagging slices in eight of the 20 T2DM subjects. The reason for the data loss is likely to be due to the multi-breath hold sequence used to obtain high temporal resolution tagging images. This sequence may be prone to error if the end-expiration phase is not consistent and the apical slice is particularly prone to this effect as the volume of tissue is small and susceptible to partial volume effects. However, when the data from those with complete datasets was analysed, the same progressive decrease in PEDSR from LC to OC to T2DM was demonstrated, although the difference between the T2DM and OC just failed to reach statistical significance.

The finding of increased left ventricular mass together with the borderline higher mass/volume ratio suggests that the T2DM patients in this study have evidence of

concentric, rather than eccentric remodelling. Concentric remodelling (increased mass/volume ratio) is typical of diabetic cardiomyopathy and has been associated with an increased risk of future cardiovascular events in the large population based CMR Multi-Ethnic Study of Atherosclerosis (MESA), especially in those younger than 65 years (Cheng et al. 2009). The finding of concentric remodelling contrasts with previous echocardiography studies in adolescents with T2DM which have found increased left ventricular volumes compared to controls, which combined with an increased LVM suggests a pattern of eccentric remodelling (Shah et al. 2011, Whalley et al. 2009). The differences in findings may reflect the older age of our participants who have a pattern of remodelling which is in keeping with the findings in older adults (>50 years) with T2DM (Shah et al. 2011). Furthermore, the differences may also be explained by the fact that CMR, a 3-dimensional technique, does not rely on geometric assumptions to calculate volumes and mass compared to echocardiography (Grothues et al. 2002).

Overall, these CMR findings combined with the adverse cardiovascular risk status suggest that young patients with T2DM are already on a downwards spiral to developing cardiac complications. Indeed the marked reduction in diastolic strain rate and the borderline significant reduction in peak systolic strain suggest these patients may be at risk of incipient LV systolic dysfunction. The findings would strongly support early identification and aggressive management in such subjects rather than relying on the conventional approach of considering 10 year risk of cardiovascular disease.

Numerous factors have been proposed in the pathway from over nutrition and dysglycaemia to cardiovascular dysfunction, including elevated cytokine activity, altered insulin signalling, and glyco- and lipo-toxicity and with each additional risk factor further increasing the risk of endothelial dysfunction with subsequent increases in vascular tone and myocardial oxygen demand leading to eventual diastolic dysfunction (von Bibra et al. 2010). However, the development of these abnormalities is potentially reversible. Weight loss, either through dietary restriction or bariatric surgery, can reverse diastolic dysfunction (From et al. 2010). Benefits have also been demonstrated with intensive glycaemic control, ramipril and statin therapy (Grandi et al. 2006, von Bibra et al. 2004, Dounis et al. 2006, Okura et al. 2007, Siegmund et al. 2007, Brassard et al. 2007). There are also preliminary data from animal models demonstrating improvements in systolic and diastolic function with long term GLP-1 receptor agonist therapy which holds promise for the future (Liu et al. 2010).

A high proportion of the T2DM and obese groups in this study were vitamin D deficient. The reasons for this are likely to be multifactorial. Firstly, 50% of our obese and T2DM groups were from black or minority ethnic groups, a known risk factor for vitamin D deficiency (Pearce et al 2010). Secondly, the main source of vitamin D is sunlight and it is possible that obesity is associated with a reluctance to expose skin due to embarrassment about body habitus which, combined with a suboptimal dietary intake, will lead to deficiency (Janisse et al. 2011). Finally, vitamin D is a fat-soluble vitamin sequestered by adipose tissue which reduces bioavailability in obese subjects. Vitamin D deficiency has a potential role in the pro-inflammatory state demonstrated by the T2DM and OC groups (Chagas et al. 2012). The vitamin D

receptor is ubiquitous in the immune system and plays a crucial role in immune modulation (Chagas et al. 2012). Vitamin D deficiency can therefore lead to a pro-inflammatory state and potentially predispose individuals to insulin resistance and/or T2DM.

In keeping with previous studies of younger adults with T2DM, the T2DM and OC groups had similar VO_{2max} relative to body mass (Burns et al. 2007). They also had similar, high rates of sedentary behaviour, higher than previously reported in studies of older adults and a finding which has relevance in late chapters (Chapters Five, Six Seven and Eight) (Healy et al, 2007). Exercise training has an established role in the prevention and management of T2DM, the benefits of which include improvements in weight, glycaemic control and diastolic dysfunction (Hordern et al. 2009, Umpierre et al. 2011, Boule et al. 2001). However, there is some evidence to suggest that, in contrast to obese subjects, young adults with T2DM may not respond to exercise as anticipated, failing to enhance their VO_{2max} , whole body and hepatic insulin sensitivity in response to a supervised exercise training programme (Burns et al. 2007). Furthermore, in the TODAY randomised controlled trial a large group of youth with T2DM failed to gain any additional benefit from metformin combined with a lifestyle intervention compared to metformin alone (TODAY, 2012). These studies raise the possibility of metabolic inflexibility in these young adults and it remains possible that they may not derive the same cardiovascular benefits from lifestyle interventions as have been previously witnessed in older adult populations with diabetes.

In conclusion, obesity in younger adults with and without T2DM is associated with an adverse cardiovascular risk profile. However, in addition to the effects of obesity, younger adults with T2DM also have subclinical diastolic dysfunction which supports the hypothesis that young people with T2DM will have a high risk of future cardiovascular complications. These study findings help build the case for the aggressive multidisciplinary, multi-factorial management of young people with T2DM and those at risk of developing this condition at a early age. There is a need to develop novel interventions in young people to prevent the development of T2DM and the subsequent premature cardiovascular morbidity and mortality which will be associated with this condition. Building on these findings, Chapters Five, Six, Seven and Eight will discuss the development and delivery of the Sedentary Time AND Diabetes (STAND) intervention, designed to tackle the high rates of sedentary behaviour in young individuals who are at high risk for the development of T2DM.

Table 3.1 - Participant characteristics

				p	
	Type 2 diabetes (N = 20)	Lean controls (N = 10)	Obese controls (N = 10)	Type 2 diabetes v lean	Type 2 diabetes v obese
Age (years)	31.8 (6.6)	30.0 (6.7)	30.9 (5.6)	0.477	0.699
Female (%)	45	50	60	1.000	0.700
BME (%)	50	30	50	0.444	1.000
Weight (kg) ^a	99.9 (20.3)	63.3 (8.2)	93.9 (13.0)	<0.001	0.481
BMI (kg/m ²) ^a	33.9 (5.8)	21.9 (1.7)	33.4 (2.4)	<0.001	0.618
Waist (cm) ^a	109.7 (12.6)	76.6 (7.2)	106.2 (8.1)	<0.001	0.394
Waist:Hip ^a	0.97 (0.06)	0.81 (0.07)	0.92 (0.07)	<0.001	0.082
Systolic BP (mmHg) ^a	134.8 (14.2)	129.5 (11.3)	127.1 (14.0)	0.196	0.168
Diastolic BP (mmHg) ^a	87.6 (9.8)	79.4 (12.5)	84.1 (9.1)	0.110	0.376
VO _{2max} (ml/kg/min) ^a	23.1 (5.0) ^b	42.1 (7.4)	25.2 (6.8)	<0.001	0.255

Data are mean (SD). BP, blood pressure; BME, black & minority ethnicity.

^a Results are adjusted for ethnicity and sex.

^b1 Missing value.

Table 3.2 - Fasting biochemical variables

	p ^a				
	Type 2 diabetes (n= 20)	Lean controls (n= 10)	Obese controls (n= 10)	Type 2 diabetes v lean	Type 2 diabetes v obese
Biochemical parameters					
Cholesterol (mmol/l)	4.2 (3.6, 5.3)	4.4 (3.9, 4.9)	4.2 (3.8, 5.2)	0.809 ^b	0.830 ^b
LDL (mmol/l)	2.4 (2.1, 2.9) ^d	2.4 (2.2, 3.4)	2.7 (2.0, 3.0)	0.907 ^b	0.851 ^b
HDL (mmol/l)	1.1 (0.2) ^c	1.6 (0.4)	1.2 (0.3)	<0.001	0.336
Triglycerides(mmol/l)	1.6 (1.0, 2.7)	0.8 (0.6, 1.0)	1.2 (0.9, 1.5)	0.014 ^b	0.133 ^b
HbA1c (%)	7.1 (6.7, 10.3) ^c	5.6 (5.4, 5.6)	5.5 (5.3, 5.9)	<0.001 ^b	<0.001 ^b
HOMA-IR	2.6 (1.8, 4.8)	0.9 (0.8, 1.0) ^d	1.8 (1.5, 2.5)	<0.001 ^b	0.021 ^b
Glucose (mmol/l)	8.3 (6.2, 11.9)	5.0 (4.4, 5.2)	5.1 (4.7, 5.5)	0.002 ^b	0.003 ^b
Insulin (mU/l)	16.7 (12.2, 31.8) ^c	5.0 (4.3, 6.2) ^e	13.1 (8.1, 20.9)	<0.001 ^b	0.030 ^b
C-peptide (nmol/l)	1.0 (0.7, 1.5)	0.4 (0.4, 0.5) ^d	0.8 (0.7, 1.1)	<0.001 ^b	0.086 ^b
Vitamin B12 (ng/l)	444 (143)	374 (150)	358 (108)	0.150	0.160
ALT (iu/l)	34.5 (21.5, 58.8)	26 (18.5, 27.5) ^c	25.5 (17.8, 37.8)	0.036 ^b	0.106 ^b
Vitamin D <30nmol/l (%)	85 (n=17)	30 (n=3)	80 (n=8)	<0.001	0.372
Inflammatory biomarkers					
IL-6 (pg/ml)	5.4 (2.4, 7.3)	2.3 (0.8, 3.1) ^c	4.5 (2.7, 7.1)	0.004 ^b	0.773 ^b
Adiponectin (µg/ml)	2.6 (1.7, 3.5)	6.6 (5.0, 9.8)	4.0 (2.0, 5.4)	<0.001 ^b	0.141 ^b
TNF-α (pg/ml)	1.4 (1.2, 1.7) ^d	1.0 (0.9, 1.2)	1.4 (1.3, 1.6)	0.016 ^b	0.638 ^b
IL-10 (pg/ml)	2.1 (1.3, 2.9)	0.8 (0.6, 1.1)	1.5 (1.2, 1.7)	<0.001 ^b	0.087 ^b
CRP (µg/ml)	3.2 (2.0, 5.2)	1.4 (0.3, 1.8)	3.9 (2.1, 9.8)	0.004 ^b	0.651 ^b

Data are mean (SD) or median (25th and 75th percentiles) for non-parametric distributions.

^a Adjusted for ethnicity and sex.

^b Based on transformed data

^c 1 Missing value.

^d 2 missing values.

^e 3 missing values.

Table 3.3. Cardiac Magnetic Resonance Imaging Data

	p ^a				
	Type 2 diabetes (n = 20)	Lean controls (n = 10)	Obese controls (n = 10)	Type 2 diabetes v lean	Type 2 diabetes v obese
LVM (g)	85.2 (76.4, 102.9)	80.8 (70.9, 85.5)	76.2 (65.8, 111.6)	0.002 ^b	0.601 ^b
LVMI (g/m ²)	40.0 (35.6, 45.7)	45.0 (38.0, 49.6)	38.8 (34.6, 48.4)	0.348 ^b	0.911 ^b
LVM/I/height ^{1.7} (g/m)	34.2 (30.7, 40.1)	30.7 (26.9, 35.4)	33.8 (29.0, 41.7)	0.010 ^b	0.853 ^b
LVM/LVEDV (g/ml)	0.54 (0.45, 0.61)	0.45 (0.42, 0.51)	0.54 (0.48, 0.60)	0.052 ^b	0.816 ^b
LVEDV (ml)	173.4 (33.3)	162.7 (22.5)	169.5 (35.7)	0.171	0.755
LVEDVI (ml/m ²)	79.8 (11.5)	94.2 (9.2)	80.5 (11.0)	0.004	0.949
LVEDV/height ^{1.7} (ml/m)	69.25 (11.98)	66.20 (8.06)	70.09 (11.31)	0.300	0.968
LVESV (ml)	78.3 (17.6)	72.7 (14.2)	79.7 (23.6)	0.222	0.784
LVESVI (ml/m ²)	36.0 (6.6)	41.9 (5.4)	37.6 (8.3)	0.037	0.562
LVESV/height ^{1.7} (ml/m)	29.46 (26.81, 35.64)	29.45 (25.72, 32.23)	30.99 (26.77, 39.28)	0.393	0.670 ^b
Ejection Fraction (%)	54.9 (5.0)	55.5 (3.5)	53.6 (4.5)	0.727	0.481
Tagging (global)					
PSS (%)	-21.20 (2.75)	-23.48 (2.36)	-23.30 (2.62)	0.077	0.076
PSSR (1/s)	-1.13 (0.18)	-1.20 (0.15)	-1.17 (0.20)	0.422	0.642
PEDSR (1/s)	1.51 (0.24)	1.97 (0.34)	1.78 (0.39)	0.001	0.042

Data are mean (SD) or median (25th and 75th percentiles) for non-parametric distributions. LV = left ventricular, LVM = left ventricular mass, I = indexed to body surface area, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, PSS = peak systolic strain, PSSR = peak systolic strain rate, PEDSR = peak end diastolic strain rate ^aAdjusted for ethnicity and sex. ^bBased on transformed data

Figure 3.1:Representative CMR images.

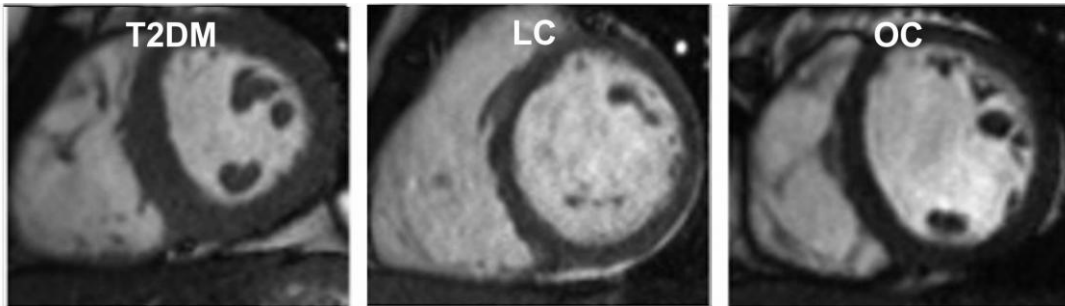


Figure 3.1.CMR images at mid-level from individuals in each of the three groups T2DM, lean controls (LC) and obese controls (OC). Images illustrate end-diastolic views demonstrating greater mass in T2DM and OC subjects compared with LC. Mass/volume were 0.74 g/ml,0.41 g/ml, 0.45 g/ml respectively. Left ventricular mass indexed to height were 53.19 g/m,26.48 g/m, 34.12 g/m respectively.

Chapter Four: Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis

Chapter Overview

This chapter introduces the concept of sedentary behaviour. In Chapter Three the young adults spent 70-75% of their time in sedentary behaviour, time spent sitting or lying which is generally associated with low energy expenditure. Physical inactivity, the absence of exercise, is an established risk factor for T2DM. However, I wanted to explore whether sedentary time, the actual amount of time spent sitting, was also associated with T2DM. To do this I embarked upon a systematic review and meta-analysis to identify the associations between excess sedentary time and T2DM, cardiovascular disease (CVD), CVD and all cause mortality. The findings of this chapter were published in Diabetologia and led to national and international media attention in the findings. The publication and details of the media interest can be found in Appendices Six and Eight respectively. This chapter also lays the foundations for the following Chapters Five to Eight which explore the development and delivery of the Sedentary Time AND Diabetes (STAND) structured education intervention designed to reduce sedentary in young adults at risk of T2DM.

Abstract

Aims: Sedentary (sitting) behaviours are ubiquitous in modern society. A systematic review and meta-analysis was performed to examine the association of sedentary time with T2DM, CVD and CVD and all-cause mortality.

Methods: Medline, Embase and the Cochrane Library databases were searched for terms related to sedentary time and health outcomes. Cross sectional and prospective studies were included. Relative risk (RR)/ Hazard ratio (HR) and 95% confidence intervals were extracted. Data were adjusted for baseline event rate and pooled using a random effects model. Bayesian predictive effects and intervals were calculated to indicate the variance in outcomes that would be expected if new studies were conducted in the future.

Results: 18 studies, (16 prospective, 2 cross sectional) were included, with 794,577 participants. 15 of 18 studies were moderate to high quality. Greatest time spent sedentary compared to the lowest time spent sedentary was associated with a 112% increase in the relative risk of T2DM (RR 2.12, 95% CrI 1.61, 2.78), a 147% increase in the relative risk of CVD events (RR 2.47, 95% CI 1.44, 4.24), a 90% increase in the risk of CVD mortality (HR 1.90, 95% CrI 1.36, 2.66) and a 49% increase in the risk of all-cause mortality (HR 1.49, 95% CrI 1.14, 2.03). The predictive effects and intervals were only significant for T2DM.

Conclusion: Sedentary time is associated with an increased risk of T2DM, CVD and CVD and all-cause mortality; the strength of the association is most consistent for T2DM.

Introduction

The hazards of high levels of sitting were first highlighted in the 1950's when Jeremy Morris identified a two fold increase in the risk of a myocardial infarction in London bus drivers compared with active bus conductors (Morris et al. 1953). In the following 60 years research has focused on establishing the links between MVPA and health, largely overlooking the potentially important distinction between sedentary (sitting) and light-intensity physical activity. The opportunities for sedentary behaviour in modern society, such as watching television (TV), sitting in a car or using the computer, are ubiquitous. As such, sedentary behaviours are an important facet of human behaviour. Objective measures have demonstrated that the average adult spends 50-60% of their waking hours in sedentary pursuits (Healy et al. 2011), with even higher rates (70-75%) reported in the young adults in the Expedition study (Chapter Three).

The term “sedentary” comes from the Latin *sedere* (“to sit”) and can operationally be defined as any waking sitting or lying behaviour with low energy expenditure. This operational definition broadly fits with the commonly cited technical definition of <1.5 metabolic equivalent units (Pate et al. 2003). The term “sedentary behaviour” therefore typically refers to sitting/lying

behaviour rather than a simple absence of MVPA (Pate et al.2008, Sedentary Behaviour Research Network, 2012)

In the past decade interest in sedentary behaviour research has been reignited. To date, two narrative systematic reviews and a meta-analysis of sedentary behaviour and health outcomes in adults have been published. The systematic reviews examined a range of outcomes, including T2DM and mortality, with both identifying moderate-to-strong evidence for an association with sedentary behaviour (van Uffelen et al. 2010, Proper et al. 2011). However, these conclusions were based on a small number of studies and did not allow for a meta-analysis to be undertaken. A meta-analysis was recently published on the association between TV viewing in adults and type 2 T2DM (4 studies), CVD (4 studies) and all-cause mortality (3 studies) (Grontved & Hu, 2011). However, although TV viewing is a common sedentary behaviour in leisure time, evidence suggests that it may not be a good representation of total sedentary time, particularly in men (Sugiyama et al. 2008).

To support the development of coherent evidence-based guidance which will inform future research and public health policy, we aimed to quantitatively synthesise existing observational evidence relating sedentary (sitting) time to four key clinical outcomes: T2DM, CVD, CVD mortality and all-cause mortality. To our knowledge, this is the first meta-analysis of sedentary behaviour and health outcomes beyond just TV viewing.

Methods

Search strategy and inclusion criteria I had one to one training with a librarian (Sarah Sutton) with extensive knowledge and experience of developing and running searches for systematic reviews. The development of an optimal search strategy was an iterative process. The term “sedentary lifestyle” was only recognised as a medical subject heading (Mesh) term in 2010. As such, comprehensive search terms had to be used in the search to reflect the most common forms of sedentary behaviour. To check that these terms were sensitive, the search was performed and then checked for the inclusion of key publications relevant to the systematic review. The search strategy also included the Mesh terms related to health outcomes and study designs. Text word, title word, abstract and subject headings were searched in addition to several non-medical subject headings to cover sedentary behaviours, T2DM, CVD and CVD and all cause mortality. The list of the search terms for the systematic review are available in Appendix Three.

To be included in the review studies had to meet the following criteria:

- Cross sectional or prospective design
- Report data on adults ≥ 18 years of age
- Include self-reported or objective measure of time spent sedentary
- Report data on a relevant health outcome: T2DM, CVD (defined as: myocardial infarction, angina, heart failure, stroke, coronary/carotid revascularisation), CVD or all-cause mortality)

Studies were not included if “inactivity” was reported as sedentary behaviour, rather than a measure of actual time spent in sedentary activities. This approach was taken because “inactivity” is used within physical activity research to define a category at the lower end of the MVPA continuum, typically a failure to meet the recommended 30 minutes of MVPA per day, rather than the absence of movement. Therefore such definitions of inactivity cannot be used to infer the amount of sedentary time undertaken (Sedentary Behaviour Research Network, 2012).

I searched OVID Medline to January week 2, 2012, Embase 1980 to 2012 week 2 and the Cochrane library from inception to January 2012. The search was limited to published articles written in English. The references of papers meeting the inclusion criteria were hand searched. Personal databases was also searched for relevant articles.

Titles and abstracts were reviewed independently by Charlotte Edwardson (CE) and I and the full text of any potentially relevant article was obtained. If any uncertainty existed, full text was obtained for discussion between CE and I. Studies which did not meet the inclusion criteria were disregarded at this stage.

Quality assessment

Members of our study team (EW, CE, Stuart Biddle, Tom Yates, Trish Gorely) developed a quality assessment tool with reference to MOOSE and STROBE (Table 4.1) (Stroup 2000, von Elm et al. 2008). The total score

available was 6 points (1 point for a prospective study design; if sedentary behaviour was self-reported 1 for reported reliability, 1 for reported validity; 2 if an objective measure of sedentary behaviour was used; 1 if 2 or more confounders were controlled for; 1 if analysis controlled for physical activity; 1 for an objective measure of the health outcome (e.g. oral glucose tolerance test versus self report to diagnose T2DM)). EW and CE independently assessed all studies for quality. Any discrepancies arising were discussed with the study team. A score of 5-6 was considered high quality, 3-4 moderate quality, 0-2 poor quality.

Data extraction and synthesis

A data extraction form was developed. I independently extracted data on the association between sedentary time and health outcomes which was cross checked with data independently extracted by CE. The measurement of time spent sedentary varied, for example, hours per day, hours per week divided into quartiles or arbitrarily divided, e.g., >4 hours per week vs. <14 hours per week. To overcome this discrepancy in reporting, we compared outcomes associated with the highest time spent sedentary time with the lowest.

Analysis Relative risk (RR) or hazard ratio (HR), and 95% confidence intervals comparing the highest level of sedentary behaviour to the lowest were extracted for each study. Where adjustment for covariates had been made the data were extracted from the model with the most comprehensive set of predictors (i.e. “most adjusted” model). However, analysis did not allow for adjustment by body mass index or waist circumference as this may have

represented a statistical overcorrection given weight status is a likely intermediate variable in the pathway linking sedentary behaviour to adverse health outcomes. If data were available for more than one type of sedentary behaviour within the same cohort then data for sitting time or television viewing were prioritised for inclusion. Where relative risks were not given, I calculated these from adjusted odds ratios where possible using the method of Zang and Yu (Zhang & Yu, 1998). Hazard ratios and incidence risk ratios were assumed to be equivalent to relative risks and vice versa. If a study did not present adjusted results in a format suitable for inclusion or conversion to a relative risk, the raw unadjusted data was used to calculate relative risk.

The Bayesian random effects meta-analysis was conducted by statisticians with expertise in this field (Laura Gray and Felix Achana). The remaining paragraphs in the methodology describe the approach employed by this team. Where data were reported for males and females they combined these using a fixed effects model and the pooled estimate was used, so that each study was included in each meta- analysis once only. Risk and/or hazard ratios were transformed onto the logarithmic scale and pooled across studies using Bayesian random effects meta-analysis (standard meta-analysis methods (classical inverse-variance) were used for CVD due to limited study numbers). In the random effects model, the association between sedentary time and health outcomes was assumed to vary from study to study. To reduce between study heterogeneity, data were adjusted for baseline event rate using the logarithm of the observed control group rate (i.e. percent of disease in participants in the low sedentary time group) (Arends et al. 2000,

Sharp & Thompson, 2000). Data are reported as mean effect hazard ratio and 95% credible intervals (Bayesian equivalent of confidence intervals).

Pooled effects from a random effects meta-analysis represent the average of individual study effects and may not accurately represent the different study populations, even where differences in event rate are controlled for, especially where levels of heterogeneity are likely to be high. Therefore, in order to comply with best practice, they obtained estimates of the study-specific “shrunk effects” and the predictive mean effect and interval. The predictive effect and interval are specifically designed to take account of heterogeneity in meta-analyses and widens the degree of uncertainty with increased heterogeneity (Ades et al. 2005, Higgins et al. 2009); they therefore give a more robust estimate of the true effect size. The predictive effect and interval are commonly conceptualised as quantifying the mean effect and variance in possible outcomes that would be expected to occur if new studies were conducted in the future.

Heterogeneity was quantified using between-study standard deviation (I^2 -statistic in the case of CVD). Publication bias was assessed by visual inspection of contour enhanced funnel plots and Egger’s test if there were at least 10 studies (Peters et al. 2008, Sterne et al. 2011). Where significant publication bias was found the Duval and Tweedie nonparametric trim-and-fill method was used to provide an estimate of the number of unpublished studies and an estimate of what the observed effect might have been had these studies been available (Duval & Tweedie, 2000). Analyses were

carried out using WinBUGS (Spiegelhalter et al. 2007). The classical inverse variance meta-analysis for the CVD outcome and assessment of publication bias were conducted using Stata version 11. Statistical significance relates to $p < 0.05$ and 95% confidence intervals/credibility intervals are quoted throughout.

Results

The search identified 4835 articles (Figure 4.1), of which 163 were potentially relevant. 145 of these were excluded for a number of reasons: inappropriate age range; inappropriate measure of sedentary behaviour (i.e. defined on a continuum of physical activity); inappropriate study design (e.g., review); data not reported on a relevant health outcome. Inclusion criteria were met in 19 studies, one of which was subsequently excluded because prospective data was available from the same cohort (Stamatakis et al. 2009). Of the remaining 18 studies, ten examined the association between sedentary time and T2DM (Dunstan et al. 2004, Hu et al. 2001, Hu et al. 2003, Ford et al. 2010, Krishnan et al. 2009, Tonstad et al. 2009, Stamatakis et al. 2011, Matthews et al. 2012, Hawkes et al. 2011, Wijndaele et al. 2011) ($n=482,117$ participants), three CVD (Stamatakis et al. 2011, Hawkes et al. 2011, Manson et al. 2002) ($n=80,221$), eight CVD mortality (Stamatakis et al. 2011, Matthews et al. 2012, Dunstan et al. 2010, Katzmarzyk et al. 2009, Patel et al. 2010, Warren et al. 2010, Wijndaele et al. 2011, Weller et al. 1998) ($n=421,921$) and eight all-cause mortality (Stamatakis et al. 2011, Matthews et al. 2012, Dunstan et al. 2010, Katzmarzyk et al. 2009, Patel et al. 2010, Wijndaele et al. 2011, Weller et al. 1998, Inoue et al. 2008) ($n=497,211$)

(Table 4.2). Two cross sectional and 16 prospective cohort studies were included from a range of countries including Australia, England, Canada, Germany, Japan, Scotland and the United States of America. Three prospective studies reported cross sectional baseline data on health outcomes which were relevant to and included in the meta-analysis (Matthews et al. 2012, Hawkes et al. 2011, Wijndaele et al. 2011). The mean age of participants in the studies ranged from 38 to 63 years. Two studies included men only, three included women only and the remaining 13 contained mixed samples. In the prospective studies, mean follow-up ranged from 3 to 21 years. All studies used a self-reported measure of sedentary behaviour. Although some studies reported data on multiple sedentary behaviours all studies reported either television/screen based entertainment and/or self-reported sitting time. These were used for the meta-analysis.

Study quality

All studies used a self-reported measure of sedentary time. Four studies (Dunstan et al. 2004, Hawkes et al. 2011, Dunstan et al. 2010, Wijndaele et al. 2011) (n=482,117 participants), made reference to the validity or reliability of this measure. The studies varied in quality, ranging from 0/6 to 6/6 (mean 4/6): 8/10 T2DM, 3/3 CVD, 7/8 CVD mortality and 7/8 all-cause mortality studies were of moderate-high quality.

Quantitative data synthesis

Greater time spent sedentary significantly increased the relative risk of T2DM (RR 2.12; 95% CrI 1.61, 2.78), CVD (RR 2.47; 95% CI 1.44, 4.24), CVD

mortality (HR 1.90; 95% CrI 1.36, 2.66) and all-cause mortality (HR 1.49, 95% CrI 1.14, 2.03) (Figure 4.2, Table 4.3). The predictive hazard ratio in a new study was 2.19 (95% CrI 1.05, 4.25) for T2DM, 1.90 (95% CrI 0.82, 4.39) for CVD mortality and 1.46 (95% CrI 0.93, 2.24) for all cause mortality. The CVD results were not adjusted for baseline risk and therefore do not have an associated predictive hazard ratio as the small number of studies did not allow for meaningful adjustment. There was no evidence of a significant association between the hazard ratio and baseline risk of T2DM (regression coefficient 0.79; 95% CrI -0.22, 1.92), CVD mortality (regression coefficient -0.16; 95% CrI -0.65, 0.35) and all-cause mortality (regression coefficient 0.12; 95% CrI -0.20, 0.38). Limiting the analysis to studies which controlled for physical activity as a covariate decreased the precision with which pooled risk ratios were estimated but not enough to change overall conclusions (Table 4.3).

Publication Bias and Heterogeneity

There was evidence of significant publication bias for T2DM (Eggers test $t=6.12$, $p\leq 0.001$), which would suggest that unpublished negative findings from smaller studies may exist. However, adjusting the results to account for this did not significantly alter the conclusions reached (RR 2.12, 95% CI 1.61, 2.78). Publication bias was not assessed for CVD and the mortality outcomes as there were less than 10 studies for each of these outcomes. The between-study standard deviation in the log-risk ratio (Table 4.3) was 0.28 (95% CrI 0.12, 0.61) for T2DM, 0.28 (95% CrI 0.07, 0.82) for CVD mortality and 0.12 (95% CrI 0.04, 0.32), representing moderate to high degree of heterogeneity

for the respective outcomes. Heterogeneity was low for the CVD outcome (I² 55.9%, $p=0.104$).

Discussion

Higher levels of sedentary behaviour are associated with a 112% increase in the relative risk of T2DM, 147% increase in the risk of CVD, 90% increase in the risk of CVD mortality and 49% increase in the risk of all-cause mortality. Based on the pooled estimates alone, greater sedentary time is significantly associated with an increased risk of T2DM, CVD, CVD and all cause mortality. The Bayesian predictive effect and interval were only significant for T2DM indicating that the association between sedentary time and T2DM is stronger than for mortality outcomes.

Previous narrative systematic reviews have evaluated sedentary time and health outcomes. Van Uffelen et al examined the relationship between occupational sitting and health outcomes including T2DM, CVD and mortality (van Uffelen et al. 2010). They found an association between occupational sitting time and T2DM in two of three prospective studies, and in one cross-sectional study. For mortality, they reported that four prospective studies found an association with an increased mortality risk, while one study found no association, and one study found that sitting was associated with a decreased mortality. Proper et al conducted a review of prospective studies and sedentary behaviours (Proper et al. 2011). They found moderate evidence for an association between sedentary behaviour and T2DM and strong evidence for a relationship between sedentary behaviour and CVD

and all-cause mortality; however the strength of the evidence was not quantified. Many of the studies included in these reviews did not meet our strict inclusion criteria of a measure of the time spent in sedentary behaviours. Both reviews therefore included some studies that defined sedentary behaviour as an absence of MVPA. Such comparisons only confirm what we already know – that MVPA is beneficial for health.

The recent meta-analysis of the relationship between TV viewing and health outcomes, specifically risk of T2DM, CVD and all-cause mortality, included rather few studies and was restricted to only one sedentary behaviour (Grontved & Hu 2011). TV viewing has been shown to be a poor measure of overall sedentary behaviour, particularly in men, therefore TV viewing may underestimate the true effect of overall sitting-related sedentary behaviour on health outcomes.

The present meta-analysis demonstrates strong and consistent associations between sedentary time and T2DM, CVD and CVD and all-cause mortality; the reported associations were largely independent of physical activity, adding further weight to the concept of sedentary behaviour being a distinct behaviour in its own right. This is an important conclusion because it suggests that the deleterious effects of higher levels of sedentary behaviour are not mediated through lower amounts of MVPA. This observation is consistent with other measurement studies. For example, MVPA and markers of sedentary behaviour, such as TV viewing have been shown to be weakly correlated ($r < 0.3$), and cluster analytic studies in young people have

shown separation between active and sedentary behaviours (Marshall et al. 2002). Studies of temporal patterning of sedentary behaviour demonstrate that MVPA and single sedentary behaviours compete for time at limited periods during the day, and show that over 24 hours there is time for both (Biddle et al. 2009). However, in contrast, sedentary behaviour is strongly inversely associated with time spent in light physical activity, such as standing and light ambulation (Healy et al. 2008). Therefore, on a population level, sedentary time is not commonly displaced with MVPA, but with higher levels of light-intensity physical activity. Confusion and misuse of terms related to sedentary behaviour has led to a recent consensus statement from the international Sedentary Behaviour Research Network (2012). Our study therefore suggests that substituting sedentary behaviour for standing or light-intensity physical activity may reduce the risk of chronic disease and mortality, independently to the amount of MVPA undertaken.

Studies of lipoprotein lipase regulation have identified a potential pathway through which inactivity results in some of the negative metabolic consequences identified in this meta-analysis. Enforced immobility in rats leads to a demonstrable reduction in postural muscle lipoprotein lipase activity. This is important as reduced lipoprotein lipase has previously been associated with blunted triglyceride uptake, reduced plasma HDL levels and CVD (Hamilton et al. 2008). Furthermore, MVPA has little impact of lipoprotein lipase activity in comparison to inactivity, highlighting the importance of postural muscle contraction activation (Hamilton et al. 2008,

Bey et al. 2003). Lipoprotein lipase is the first protein to be identified in the cellular pathway from muscular inactivity to adverse metabolic sequelae.

This meta-analysis identified a strong association between sedentary time and T2DM. There are a number of reasons why this is the case. T2DM and prediabetes are characterised by peripheral insulin resistance. Skeletal muscle is the largest insulin sensitive organ in the body, accounting for 80% of insulin stimulated glucose disposal. Insulin sensitivity in skeletal muscles is dynamic and data from rodent studies demonstrate that immobility quickly leads to significant peripheral resistance (Bey et al. 2003, Seider et al. 1982). In addition, human bed rest studies show that inactivity results in metabolic consequences which include insulin resistance and dysglycaemia (Hamburg et al. 2007). Interestingly, there appears to be a specific genotype which is particularly susceptible to the adverse effects of immobility. When those with a specific T-allele of the TCF7L2 gene (the most significant T2DM susceptibility gene) are exposed to bed rest conditions, they fail to increase their insulin secretion to overcome the insulin resistance induced by muscular inactivity (Alibegovic et al. 2010). Therefore, not only is there a unique metabolic pathway through which inactivity acts, but there is also a potential gene-environment interplay which determines who is most susceptible to developing T2DM when exposed to excess sedentary time. However, bed rest studies do not reflect typical human behaviour and experimental studies are now starting to focus on the impact of prolonged sitting. Just one day of prolonged sitting results in a significant increase in postprandial glucose and insulin (Stephens et al. 2011). Recently, Dunstan et al. demonstrated that

breaking up periods of prolonged sitting with 2 minute bouts of light intensity activity every 20 minutes results in a 24% reduction in post prandial glucose area under the curve and a 23% reduction in insulin area under the curve, compared with uninterrupted sitting (Dunstan et al. 2012). The reductions in glucose and insulin were similar for both light activity and moderate activity conditions, providing support for our finding that the relationship between sedentary time and T2DM is independent of MVPA. In further support of this finding, more recent studies of skeletal gene expression have identified that light physical activity, compared with sedentary activity, is associated with anti-inflammatory pathways, lipid and carbohydrate metabolism leading to the proposal that sedentary time may result in reduced fatty acid transport in skeletal muscle with the subsequent accumulation of intracellular fatty acids and less GLUT4 glucose transporter translocation, leading to reduced insulin induced glucose uptake (Latouche et al. 2012, Lammers et al. 2012). From the evidence available, it would appear that excess sitting has a rapid deleterious impact on insulin resistance and glycaemia, explaining the strong and consistent associations between sedentary time and T2DM in the large epidemiological studies included in our meta-analysis.

The main strengths of the review were the use of large population based datasets from a range of countries and the subsequent methods used to analyse the data. Given the diverse studies included, potential for heterogeneity in the analysis was high. This was accounted for in several ways. For example, the large variations in health outcome event rates (e.g.

T2DM 12.6% (Hawkes et al. 2012) vs. 2% (Hu et al. 2001) were taken into account by adjusting our analysis for event rates.

Each study adjusted for a different set of potential confounders, therefore we opted to use the most adjusted model, prior to adjustment for body mass index or waist circumference which are thought to act as intermediaries in the relationship between sedentary time and health outcomes. Despite variations in the type of sedentary behaviour (e.g. television time (Dunstan et al 2004), vs. sitting time Katzmarzyk et al. 2009), the measurement of sedentary behaviour within each type (e.g. sitting almost all of the time Katzmarzyk et al. 2009) vs. ≥ 6 hours per day (Patel et al. 2010)) and the geographical location (e.g. America (Matthews et al. 2012) vs. Japan (Inoue et al. 2008)) the direction of the association between sedentary time and health outcomes was consistent. Importantly, such heterogeneity was taken into account in our estimation of the association between sedentary time and health outcomes through calculating the predictive effect and interval (Higgins et al. 2009). However, there are some important limitations to consider, one of which is the high reliance on self-reported data. Self-reported sedentary time, in concordance with self-reported behaviour in general, is likely to have poor validity which would act to weaken the association with health outcomes (Clark et al. 2009). Other limitations include: 1) the use of studies published in English only. 2) The use of cross sectional data. However, the strong association between sedentary time and T2DM in the cross sectional papers remains significant in the prospective studies, although it is somewhat attenuated. 3) Causality cannot be inferred

from these results and reverse causality remains a possibility. This meta-analysis highlights the need for researchers to standardise measures of sedentary time in future studies. There is also the need to continue the current trend towards more objective measures of sedentary behaviour such as accelerometer or posture measures. Nonetheless, this is the first meta-analysis to systematically quantify the strength of association between sedentary behaviour (beyond just TV viewing) and health outcomes and our findings consistently demonstrate a strong association between sedentary time and adverse health outcomes, particularly T2DM.

In conclusion, the findings of this meta-analysis have important implications for future research and public health guidance. These findings, combined with the preliminary experimental findings by Dunstan et al. (Dunstan et al. 2012), suggest that reducing sedentary time may have a significant role in T2DM prevention. There is an urgent need to further investigate the impact of reducing sedentary time on metabolic health. Currently, evidence for the deleterious effects of sedentary behaviour are based on cross-sectional or other observational designs. Moreover, little is known about how best to change sedentary behaviour in adults as nearly all of the intervention work has been with young people and sedentary screen time (Biddle et al. 2011). Developments are therefore required for adults, in particular, structured education approaches to decreasing sedentary behaviour in the context of T2DM prevention to promote less sitting (Wilmot et al. 2011). Such an approach, project STAND (Sedentary Time ANd Diabetes), is described in detail in following chapters of this thesis. Future T2DM prevention

programmes should consider promoting reduced sedentary behaviour alongside more traditional lifestyle behaviours such as increased MVPA and dietary change.

The work presented in this chapter, published in *Diabetologia*, attracted a vast amount of national and International media attention. The details of some of this media interest can be found in Appendix Eight.

Table 4.1. Quality Score Tool used to assess eligible papers

Criteria	0 points	1 point
Study design	Cross sectional	Prospective
Validity of SB self report	Not reported	Reported validity
Reliability of SB self report	Not reported	Reported reliability
Objective measure SB	No	Yes (don't mark self report if objective measure in study)
		2 points
Adjustment for confounders	No	≥2 confounders controlled for
Adjustment for PA	No	Adjusted for PA
Adjustment for weight status	No	Adjusted for BMI

Table 4.2. Characteristics of cross sectional and prospective cohort studies included in meta-analysis.

BMI = body mass index, PA = physical activity, FHx= family history, TV= television, WC= waist circumference, DM= diabetes mellitus. ^a cross sectional baseline data used from prospective study, ^b unadjusted data used in meta-analysis. "6" is the highest quality as defined in the methods.

Author	Design, sample size	Outcome (s)	Sedentary measure used in meta-analysis (s)	Confounders measured	Quality
Dunstan 2004	Cross sectional 8,299 Australian men and women	Diabetes 252 cases (3%)	Television viewing >14 vs <14 hr/wk	Adjusted for age, education, FHx DM, smoking, diet and PA	5
Dunstan 2010	Prospective 6.6 yr f/u 8,800 Australian men and women	CVD mortality 87 cases (1%) All cause mortality 284 cases (3.2%)		Adjusted for age, sex, smoking, education, diet.	6
Ford 2010	Prospective 7.8yr f/u 23,855 German men and women	Diabetes 927 cases (3.9%)	Television viewing <1 vs.>4 hr/day	Adjusted for age, sex, education, occupational activity, smoking, alcohol, PA, diet, systolic blood pressure.	3
Hawkes 2011	Prospective 3 year f/u 1,966 Australian men and women	Diabetes 247 cases (12.6%) ^a CVD 32 cases (3.4%)	Television viewing <2 vs. >4 hr/day	Sex, age, education, marital status Diabetes outcome ^b	4
Hu 2001	Prospective 10 yr f/u 37,918 American men	Diabetes 767 cases (2%)	Television viewing >40 vs. <1 hr/wk	Adjusted for age, time, smoking, FHx DM, alcohol, PA.	3
Hu 2003	Prospective 6 year f/u 68,497 American women	Diabetes 1,515 cases (2.2%)	Television viewing >40 vs. <1hr/wk	Adjusted for age, hormone use, alcohol, smoking, FHx DM, PA, diet.	3
Inoue 2008	Prospective 8.7 yr f/u 83,034 Japanese men and women	All cause mortality 4,564 cases (5.5%)	Self report sitting time <3 vs. >8 hr/day	Adjusted for age, area, occupation, DM, smoking, alcohol, BMI, diet, exercise, sedentary activity, walking or standing hours, and leisure-time sports or physical exercise ^b	4

Table 4.2 (cont)

Katzmarzyk 2009	Prospective 12 yr f/u 17,013 Canadian men and women	CVD mortality 759 cases (4.5%) All cause mortality 1,832 cases (10.8%)	Self report sitting time Almost none of the time vs. almost all of the time	Adjusted for age, smoking, alcohol, leisure time PA	4
Krishnan 2009	Prospective 10 yr f/u 45,668 Black American women	Diabetes 2,928 cases (6.4%)	Television viewing >5 vs <1 hr/day	Adjusted for age, time FHx DM, education, family income, marital status, cigarette use, alcohol, energy intake, coffee consumption, vigorous PA, walking.	3
Manson 2002	Prospective 3.2 yr f/u 73,743 American women	CVD 1,551 cases (2.1%)	Self report sitting/lying/slee ping <4 vs. >16 hr/day	Adjusted for age and energy expenditure	3
Matthews 2012	Prospective 8.5 year f/u 240,819 American men and women	Diabetes 15,942 cases (6.6%) ^a CVD mortality 4,684 cases (2%) All cause mortality 17,044 cases (7%)	Television viewing <1 vs. ≥7 hr/day	Age, sex, race, education, smoking, diet, PA.	6
Patel 2010	Prospective 14 year f/u 53,440 American men and women	CVD mortality 6,369 cases (11.9%) All cause mortality 19,230 cases (2.8%)	Self report sitting time <3 vs. ≥6 hr/day	Adjusted for age, marital status, education, smoking, BMI, alcohol, caloric intake, co- morbidities score and PA ^b	4
Stamatakis 2011	Prospective 4.3 yr f/u 4,512 Scottish men and women	Diabetes 279 cases (6%) CVD 422 cases (9.3%) CVD mortality 215 cases (4.8%) All cause mortality 325 cases (7.2%)	Television and screen based entertainment <2 vs. ≥4 hrs/day	Unadjusted Adjusted for age & sex Unadjusted Adjusted for age & sex	4

Table 4.2 (cont)

Tonstad 2009	Cross sectional 60,903 American and Canadian men and women	Diabetes 3,430 cases (5.6%)	Television viewing <1 vs. >3 hr/day	Adjusted for age, sex, ethnicity, PA, education, income, sleep, alcohol, diet.	2
Warren 2010	Prospective 21 yr f/u 7,744 American men and women	CVD mortality 377 cases (4.9%)	Television and car use <11 vs. >23 hr/wk	Adjusted for age.	4
Weller 1998	Prospective 7 yr f/u 6,620 Canadian women	CVD mortality 159 cases (2.4%) All cause mortality 449 cases (6.8%)	Self report sitting time >1/2 the time vs. <1/2 the time	Unadjusted	2
Wijndaele 2011	Prospective 9.5 yr f/u 13,197 British men and women	CVD mortality 373 cases (2.8%) All cause mortality 1,270 cases (9.6%)	Television and video viewing <2.5 vs. >3.6 hr/day	Adjusted for age ^b	6
Wijndaele 2011	Prospective study with cross sectional data 12,608 British men and women	Diabetes 341 cases (2.8%)	Television and video viewing <2.5 vs. >3.6 hr/day	Unadjusted	0

Table 4.3: The association between sedentary time and T2DM, CVD and CVD and all cause mortality. The referent group is the lowest sedentary time. Hazard ratio/ relative risks of greater than 1 suggest that high sedentary time is harmful.

	N studies	Mean control group event rate (%)	Pooled RR/HR (95% CrI)	Predictive risk ratio new study (95% CrI)	Regression coefficient for baseline effects (95% CrI) †	Heterogeneity statistics		
						Between-study SD in log-event rate (95% CrI) †	I ² (%)	P-value
T2DM ^a	10	2.3	2.12 (1.61, 2.78)	2.19 (1.05, 4.26)	0.79 (-0.22, 1.92)	0.28 (0.12, 0.61)	-	-
Cohort ^a	5	~	1.93 (1.40, 2.84)	1.92 (0.93, 4.34)	-	0.15(0.01, 0.92)	-	-
Cross-sectional ^a	5	~	2.36 (1.30, 4.09)	2.35 (0.64, 8.15)	-	0.33 (0.02, 1.24)	-	-
CVD ^a	3	7.8	2.47 (1.44, 4.24)	-	-	-	55.9	0.104
CVD mortality	8	1.7	1.90 (1.36, 2.66)	1.90 (0.82, 4.39)	-0.16 (-0.65, 0.35)	0.28 (0.07, 0.82)	-	-
All-cause mortality	8	5.6	1.49 (1.14, 2.03)	1.45 (0.93, 2.44)	0.12 (-0.20, 0.38)	0.12 (0.04, 0.32)	-	-
Adjusted for physical activity								
T2DM ^a	6	2.3	2.47 (1.49, 3.95)	2.47 (0.80, 7.33)	1.60 (-1.47, 4.47)	0.31 (0.03, 1.12)	-	-
CVD ^a	-	-	-	-	-	-	-	-
CVD mortality	5	1.7	1.71 (1.08, 2.48)	1.72 (0.65, 4.23)	-0.05 (-0.62, 0.49)	0.26 (0.03, 1.05)		
All-cause mortality	5	5.6	1.40 (0.45, 3.82)	1.41 (0.24, 7.27)	0.17 (-0.62, 0.98)	0.36 (0.01, 1.37)	-	-

^aRelative Risk is the effect estimate †Estimated from Bayesian random effects model; CrI = 95% credible intervals are Bayesian equivalence of 95% confidence intervals, SD = Standard deviation

Figure 4.1. Study Selection

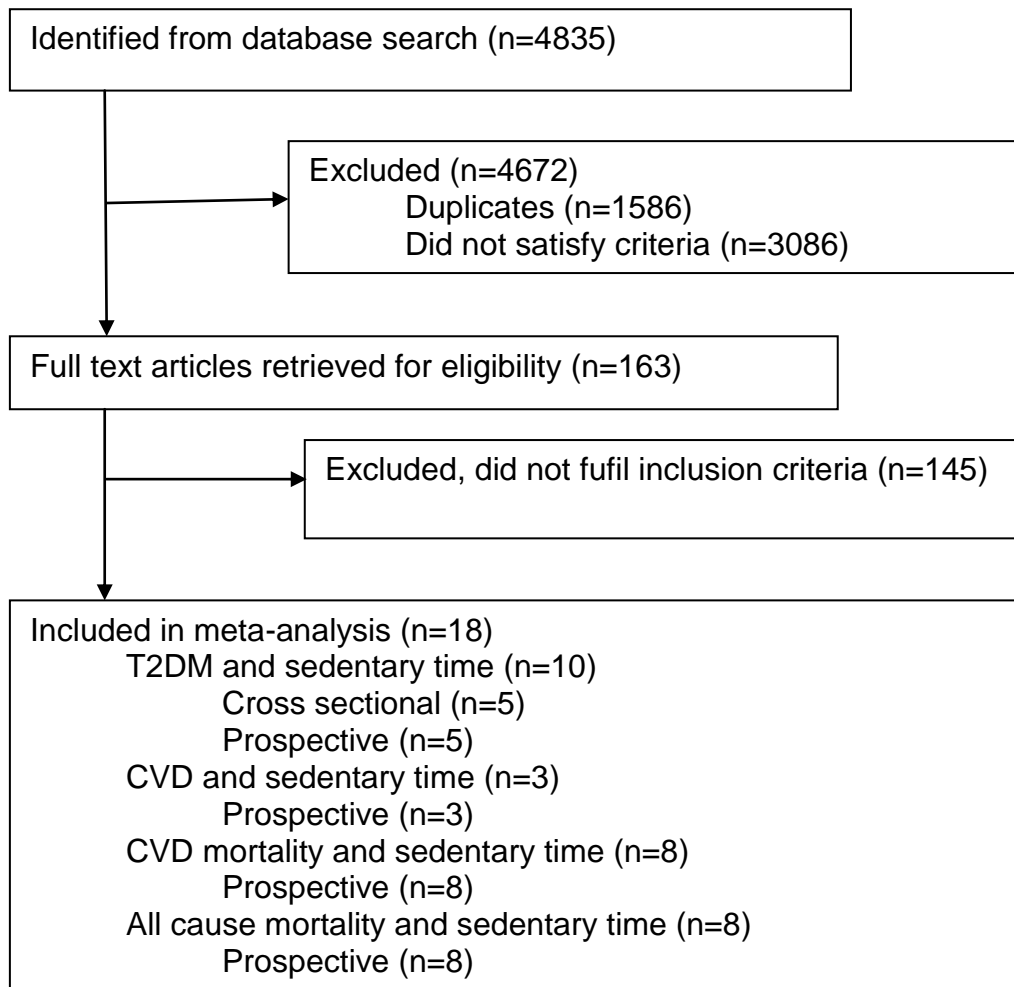
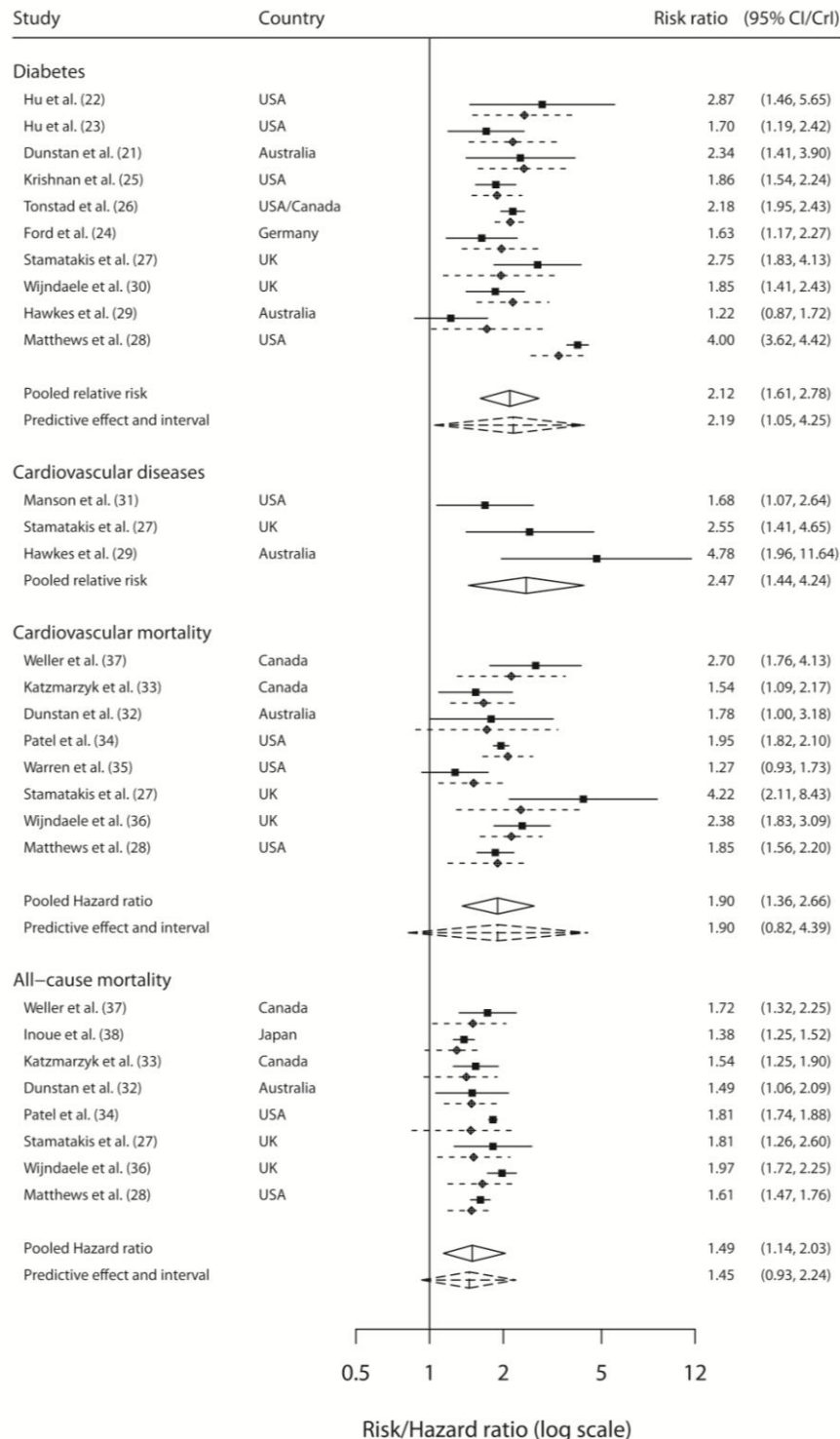


Figure 4.2. Forest Plot: the association between sedentary time and health outcomes, adjusted for baseline event rate.

The reference group is the lowest sedentary time group. Hazard ratio (HR) and relative risk (RR) greater than 1 suggests that high sedentary time is harmful. Solid lines indicate estimated HR/RR with 95% confidence intervals (CI); dotted lines indicate 'shrunken' study-specific estimates with 95% credible interval (CrI). Diamonds indicate pooled and predictive HR/RR with associated 95% CI/CrI. Cardiovascular disease was not adjusted for baseline event rate due to the small number of studies for this outcome, hence no predictive effect and interval.



Chapter Five: Project STAND: rationale, development and pilot of the intervention

Chapter overview

As highlighted in Chapters Two and Three, the prevalence of T2DM in young people is increasing and this is likely to result in excess morbidity and mortality. Chapter Four showed that excess sedentary time is a risk factor for the development of T2DM, independent of the amount of physical activity undertaken. Chapter Five incorporates the issues of the increasing prevalence of T2DM in young people and the role of excess sedentary time in the aetiology of this condition. Here I describe the rationale and methodology of project STAND (Sedentary Time ANd Diabetes). Once funding was successfully secured from the Medical Research Council National Prevention Research Initiative, I developed the protocol for the study, developed all the participant documents and led on the Research Ethics Committee and Research and Development applications. I was project manager for the delivery of all phases of this comprehensive programme of work, led the intervention development and managed the logistics of the randomised controlled trial. STAND aims to reduce sedentary time in young adults at risk of T2DM. The study is split into three phases. STAND phases 1 and 2 comprise qualitative data collection and analysis leading to the development and piloting of an evidence based structured group self-management education programme. Phase 3 is the delivery of the STAND randomised controlled education and lifestyle intervention trial. This 2-arm parallel randomised controlled trial (RCT), with 12 month follow-up, aims to

compare the effectiveness of structured education and self-monitoring (intervention) with usual care (control arm). This chapter describes the rationale for project STAND and phases 1 and 2, the development of the group structured education programme, including the psychological theories underpinning it, and the subsequent piloting of this intervention. Phase 3, the STAND randomised controlled trial methodology and results are described in Chapters Six, Seven and Eight.

Background and rationale for undertaking the STAND RCT

As outlined in Chapters Two and Three, the development of T2DM at a young age has far reaching implications. Traditional lifestyle interventions have so far failed, on a population level, to reverse the obesity and T2DM epidemic facing modern society. There is a need for novel approaches to behavioural modification to prevent the premature development of T2DM. As identified in my systematic review and meta-analysis (Chapter Four), excess sedentary time doubles the risk of T2DM, independent of the amount of moderate-to-vigorous physical activity (MVPA) undertaken (Wilmot et al. 2012). This is an important finding as, to date, public health messages have generally focused on consumption of a healthy diet and ensuring adequate amounts of MVPA are undertaken, overlooking the 50-70% of waking hours spent in sedentary pursuits (Healy et al. 2007).

However, the association between sedentary time and T2DM which was identified in the meta-analysis in Chapter Four was based on epidemiological data and cannot be used to infer causality. To assess causality, it is helpful to

consider Hill's criteria (Hill 1965). Table 5.1 (next page) describes these criteria with an indication whether they are met for the relationship between sedentary behaviour and T2DM.

The appraisal data presented in Chapter Four of my thesis supports the majority of Hill's criteria for causation. However, the main gap in Table 5.1 is for 'experiment' support. Hill postulated that a causal interpretation of an association from a non-experimental study was supported if a randomised trial confirmed the finding (Hill, 1965). Following a search of the literature, there have been no randomised long term intervention studies in young adults to investigate, first, whether a reduction in sedentary time is possible and, secondly, whether any change in sedentary time is associated with health benefits in young people at risk of T2DM.

STAND Hypothesis

The primary hypothesis of the STAND study is that group structured education can be used to decrease sedentary behaviour in young adults at risk of T2DM. The secondary hypothesis is that reducing sedentary behaviour will result in favourable changes in key behavioural and biological markers of T2DM risk.

Table 5.1 Hill's Criteria (1965) for causality: sedentary behaviour & T2DM

Hill's Criteria	Explanation	Sedentary behaviour and T2DM
Strength of association	The larger the association the more likely that it is causal	Large association between sedentary time and T2DM (Chapter Four)
Consistency	Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect	Consistent relationship between sedentary time and T2DM (Chapter Four)
Specificity	Causation is likely if a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.	Not supported. Difficult to ascertain because the aetiology of T2DM is multi-factorial (Chapter Two)
Temporality	Does the exposure precede the outcome?	Prospective epidemiological studies confirm a consistent temporal relationship (Chapter Four)
Biological Gradient	Greater exposure, greater incidence of effect (dose response)	Biological gradient identified in many of the studies included in Chapter Four
Plausibility	A plausible mechanism between cause and effect provides support for possible causality	Lipoprotein Lipase identified as a plausible metabolic pathway linking excess sedentary time and the metabolic consequences (Chapter Four)
Coherence	Coherence between epidemiological and laboratory findings increases the likelihood of an effect.	Coherence between laboratory (human bed rest and sitting studies) and epidemiological data examining the relationship between sedentary time and glucose (Chapter Four)
Experiment	Causation is more likely where the evidence is based on randomised experimental designs	No evidence currently available
Analogy	The effect of similar factors may be considered	Physical inactivity has been identified as a risk factor for T2DM

Background to the development of the STAND curriculum

Project STAND encompasses three distinctive phases which were informed by the MRC framework for complex interventions (Craig et al. 2008). Phase One is qualitative data collection and analysis to assess the feasibility and acceptability of a sedentary behaviour intervention; Phase Two is the curriculum development and piloting of the group structured education programme; Phase Three is the STAND randomised controlled trial to assess the effectiveness of the structured education programme in reducing sedentary behaviour in young adults at risk of T2DM.

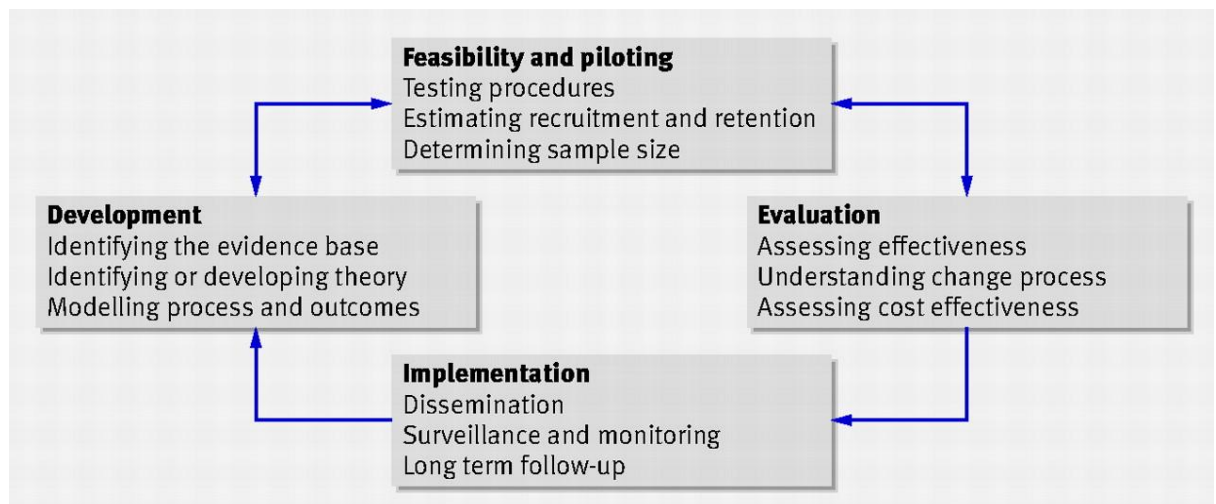


Figure 5.1. MRC framework for complex interventions (Craig et al.2008).

This framework describes how evidence, theory, modelling, and exploratory trials should be used iteratively to develop complex interventions. Importantly this framework also states that complex interventions sometimes need to be adapted to local circumstances rather than being completely standardized; therefore, we will tailor the STAND structured education programme to the needs of our target cohort.

PREPARE and DESMOND approaches to structured education

Structured patient education forms the core of the STAND intervention and is based on the Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) study (Davies et al. 2008) and related interventions such as Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE) (Yates et al. 2008) and Walking Away (Yates et al. 2012) structured education programmes which are consistent with NICE guidance (NICE 2003, 2011).

NICE have specified that patient education programmes should meet the following criteria laid down by the Department of Health and the Diabetes UK Patient Education Working Group:

- Any programme should be evidence-based, and suit the needs of the individual. The programme should have specific aims and learning objectives.
- The programme should have a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down.
- The programme should be delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the learners, and who are trained and competent to deliver the principles and content of the programme.

- The programme should be quality assured, and be reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.
- The outcomes from the programme should be regularly audited.

DESMOND is a structured education programme designed for people with recently diagnosed T2DM which meets the NICE quality criteria. This is a six hour programme, delivered by health care professionals, which aims to educate individuals on core aspects and perceptions of T2DM. DESMOND has undergone extensive piloting and has been evaluated in a multicentre cluster randomised controlled trial which demonstrated improvements in weight loss, smoking cessation, and health beliefs (Davies et al. 2008). The programme is a nationally recognised success and has been rolled out in over 50% of Primary Care Trusts.

PREPARE was a randomised controlled trial designed to assess the effectiveness of a 3 hour pragmatic structured education intervention in adults with impaired glucose tolerance. The education intervention targeted knowledge and perceptions of T2DM risk and increased walking activity. There were three arms in this trial: structured education plus pedometer for self-monitoring of physical activity; structured education only and a control arm. This intervention successfully reduced fasting and 2 hour glucose values in the arm which received both structured education and a pedometer for self-regulation. The success of the PREPARE programme has resulted in funding for the Walking Away trial which is a large 3 year follow-up cluster

randomised trial delivered in a primary care setting, designed to assess the long term effectiveness of this T2DM prevention programme (Yates et al. 2012).

The successful DESMOND and PREPARE programmes are both based on group structured education programmes, an education approach which has been identified as cost effective for use within the NHS (Gillett et al. 2010). For this reason, a similar approach was employed for the STAND intervention. If successful, STAND could also be rolled out within the NHS using existing infrastructure. DESMOND, PREPARE and STAND are all designed to address issues related to T2DM. However, unlike the STAND intervention, DESMOND and PREPARE were designed for the older adult and did not take into account the specific issues facing younger adults. For the STAND intervention there was a need to develop an effective lifestyle self management programme for younger adults at risk of T2DM, incorporating the emerging evidence on sedentary behaviour and its associated negative health outcomes. The STAND education programme was therefore developed through modifications of existing programmes to focus on reducing sedentary behaviour and the specific needs of younger adults.

Both the DESMOND and PREPARE structured education programmes encouraged patients to participate in an active way in their learning about T2DM and associated risk behaviours through non-didactic led educational workshops that included group discussions, experiential learning and practice, self-monitoring and goal setting to promote self-efficacy and

behaviour change (Lawton et al. 2010). To this end, it was important to base the STAND intervention on similar sound behavioural theories (Bartholomew et al. 2006).

Behaviour change theories

The key theories employed in the STAND structured education intervention were Bandura's Social Cognitive Theory, Gollwitzer's implementation intentions (Gollwitzer, 1999), Leventhal's Common Sense Model of Illness (Leventhal, 1980) and Dual Processing Theory (Chaiken, 1980). These theories were identified by the DESMOND collaborative following detailed intervention mapping (Bartholomew et al, 2001) and were subsequently successfully employed by both the PREPARE and DESMOND trials and are in keeping with the psychological concepts recommended by NICE for the development of behaviour change programmes. An additional theory, with particular relevance to reducing sedentary behaviour, is behavioural choice theory (Epstein et al. 2001) which is also briefly described. The following presents an overview of the theories employed in the STAND curriculum development. A summary is also presented in Table 5.2.

Social Cognitive Theory

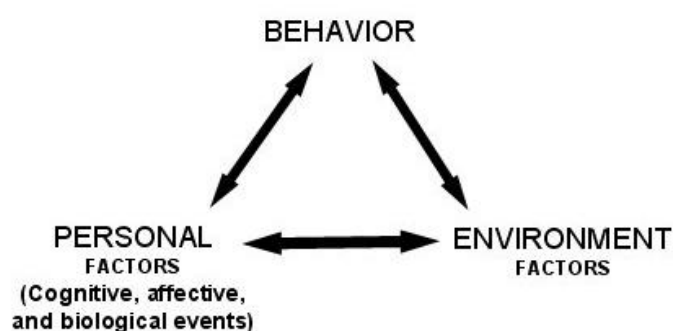


Figure 5.2. Bandura's Social Cognitive Theory (Bandura, 1986)

Bandura's Social Cognitive Theory (SCT), focuses on the concepts of self-efficacy (confidence to undertake the behaviour), targeting barriers and self-regulating behaviour (Bandura, 1986). The theory explains why people start and continue with certain behaviours and is therefore key to an intervention such as STAND. SCT proposes that behaviour is influenced by current behaviour, personal factors and environmental factors (Figure 5.2). Personal factors include internal factors such as cognitive, affective and biological states, while environmental factors include the physical and social environment. Bandura believed that the individual had the capacity to decide whether things happen through their own actions and that this will be influenced by how the individual feels, thinks and believes. Central to this is the concept of self-efficacy, defined as a person's judgment of their capabilities to organise and execute courses of action required to attain designated types of performances (Bandura 1986) – in other words, confidence to undertake a specific behaviour.

Self-efficacy

There are four central sources of self-efficacy:

- 1) **Vicarious learning** is the process of learning from other people's behaviour and works through people observing the behaviours of others and reproducing the same actions. Individuals can learn from others mistakes, gain confidence, and improve their performance from observing others.

- 2) **Prior behaviour and mastery** is the process where success is facilitated by helping the individual to achieve small and incremental goals. Mastering a behaviour in small steps builds confidence and is a powerful source of self-efficacy.
- 3) **Improving physical and emotional states** relates to ensuring the individual is rested and relaxed prior to undertaking a new behaviour to create conditions conducive to success and to avoid anxiety concerning the new behaviour.
- 4) **Verbal persuasion** is providing encouragement for the individual as they attempt to achieve a behavioural change.

Outcome expectations

SCT also predicts that outcome expectations contribute to behaviour change (Bandura 1986). While efficacy expectations are concerned with beliefs to undertake the behaviour, outcome expectations are about the expected consequences (outcomes) of performing the behaviour. Outcome expectations come in three main forms:

- positive and negative physical effects that accompany the health behaviour,
- positive and negative social sanction, and
- positive and negative self-evaluative reactions to one's behaviour.

Here, positive outcomes act as incentives and negative outcomes as disincentives. Those with high self-efficacy beliefs are more likely to form

positive outcome expectations and those with low self-efficacy are more likely to form negative outcome expectations (Bandura 1986).

Barriers to change

Barriers to health behaviour change also predict and influence behaviour change (Bandura 1986). There are two types of barriers:

- personal/situational
- socio-structural

Personal/situational barriers, in the case of reducing sedentary time, might include tiredness, too much work to do which requires sitting at a computer, favourite television programme is on, etc. Socio-structural barriers might include the journey to work which can only be done by sitting in a car, or work itself which may demand hours sat in front of a computer at a desk. Personal efficacy beliefs are strongly linked to beliefs in one's capacities to overcome personal/situational barriers, for example those with high self-efficacy are more likely to view personal barriers as surmountable and those with low self-efficacy are more likely to view their attempts at overcoming personal barriers as futile and pointless (Bandura 1986).

Self-regulation

Self-regulation is fundamental to the success of health interventions (Bandura 2005). It has been recently identified as a key component in the success of both diet and physical activity interventions (Greaves et al. 2011). Although an individual may have good intentions to change their behaviour, such as reduce their sitting time, this may not be possible for many reasons,

a situation referred to as the “intention-behaviour gap” (Orbell & Sheeran 1998). Self-regulation has been identified as an important mechanism for bridging the intention-behaviour gap and recognises that intention and motivation on their own are unlikely to produce behaviour change if not accompanied by the development of self-regulatory skills (Bandura 1997, 2004).

Self-regulation operates through three sub-functions:

- self-monitoring,
- goal setting, and
- enlistment of self-incentive for personal change (Bandura 1986).

Self-monitoring provides individuals with the necessary feedback to set realistic goals. Short and long term goals can act as motivators and lead to the development of self-efficacy through the mastery of a behaviour. Incentives are important self-motivators to encourage individuals to undertake behaviour that they might otherwise put off or avoid.

Overall, SCT contains multiple psychological facets relevant to health behaviour change: self-efficacy; outcome expectations; barriers to change; self-regulation. SCT and self-efficacy in particular, have been used to predict behaviour change in various different health settings including exercise promotion and smoking cessation (Allen. 2004, Gwaltney et al. 2009). Self-regulation was also key to the successful PREPARE programme (Yates et al. 2009) and, as such, was a desired component of the STAND intervention.

Implementation Intentions

Gollwitzer's (1999) implementation intentions concept is an important framework which facilitates self-regulation. Implementation intentions allow for the development of successful strategies around self-regulation such as focusing on the where, when and how of planned behaviour in order to close the aforementioned gap between intention and behaviour (Gollwitzer, 1999). In contrast to SCT implementation intentions essentially delegates the control of goal-directed responses to anticipated situational cues.

Action initiation and the maintenance of goals are often difficult to achieve. Despite good intentions, people often fail to implement their intentions. Gollwitzer's model overcomes barriers such as failing to get started, distractions and falling into bad habits by using a simple "if X then Y" strategy which leads to an association between a certain situation and the opportunity for goal attainment. For instance, "if the telephone rings then I will stand up" means that the individual will associate the telephone ringing with standing and will be automatically prompted to work towards their overall goal of reducing sitting time. Concrete plans around such situations increase mental representation leading to a minimal conscious effort (strategic automaticity) to achieve goals.

Common Sense Model of Illness

In terms of the STAND intervention, the Common Sense Model of Illness Representation describes an individual's perceptions of T2DM risk and how such perceptions might alter subsequent behaviour. Perceptions of risk and

health beliefs are important in terms of how individuals respond to such threats. Leventhal's Common Sense Model (Leventhal et al. 1980) postulates that individuals conceptualize identified health threats in terms of five key components:

- 1) **Identity** – label given to the condition and symptoms associated with this label.
- 2) **Cause** – perceptions about the possible causes of the illness.
- 3) **Timeline** – the duration of illness and associated symptoms.
- 4) **Consequences** – perceptions about the impact of the illness on physical and emotional health, quality of life.
- 5) **Curability/controllability** – whether the condition can be cured or controlled and views on the impact of the individuals role in this process.

The way individuals develop a cognitive representation of the illness depends on a number of potential sources of information:

- 1) **Lay information** – information gained through social contacts and media sources
- 2) **Significant others** – family, friends, doctors, nurses etc
- 3) **Previous experience** – based on existing knowledge of disease impact and associated symptoms and previous experience of coping with similar health threats

The above domains ultimately influence subsequent coping behaviour (Leventhal et al. 1980). For instance, if an individual views a diagnosis of T2DM, for example as life long, uncontrollable and associated with a number

of adverse symptoms, this perception may lead to denial and avoidance. Compare this with someone who views T2DM as potentially reversible and associated with a symptom free existence, coping mechanisms are likely to be more positive. Such illness perceptions and beliefs have been closely linked to health behaviour change in individuals with T2DM (Skinner et al. 2005) and are equally relevant to the “at risk” cohort recruited for the STAND study.

Dual Processing Theory

Chaiken’s (1980) Dual Processing Theory is concerned with how people receive and process persuasive messages and therefore impacts on how key messages are conveyed within the STAND structured education programme. Individuals can process information via one of two routes: systematic processing which involves intense scrutiny, or heuristic processing, which involves more superficial thinking.

Heuristic Processing

Heuristic processing employs judgemental rules which allow for minimal cognitive effort by the recipient. Heuristic processors are likely to agree with messages conveyed by experts or significant others without questioning the message content (Eagly & Chaiken, 1993). Heuristic processing overlooks detail and allows for the cognitive processing of simple rules and messages.

Systematic Processing

Systematic processing involves close scrutiny of the information presented. It requires a greater cognitive effort than heuristic processing and involves a systematic approach to evaluating source reliability and message content. Such individuals actively attempt to comprehend the information conveyed and perform an in-depth analysis of judgment relevant information. This approach has a stronger impact on persuasion.

Systematic vs. Heuristic

The Heuristic-Systematic model postulates that both heuristic and systematic processes can occur independently within the same individual. Attitudes developed through heuristic processing will be less stable over time and more susceptible to counter arguments. When using heuristic processing, individuals may accept messages which they might otherwise have rejected had they taken time to process the validity and content of the message systematically. A heuristic approach is taken when cognitive economy is the priority over reliability. However, reliability is likely to be more important when the message directly affects the individual. How the message is communicated is also key with analytic factors such as the content of the message and the credibility of the source influencing intentions to adopt healthy behaviours (Gibbons et al. 2009). Systematic processing is also more likely when individuals actively participate in their learning.

Behavioural Choice Theory

Behavioural Choice Theory postulates that choices between behaviours are made as the result of the accessibility (ease) of the behaviour and its reinforcement value (e.g. attractiveness, enjoyment) (Epstein et al. 2001). The opportunities for sedentary behaviours are ubiquitous and often desirable so this theory, although not employed by the previous DESMOND and PREPARE programmes, was felt to be particularly relevant to understanding the reduction of sedentary time. Behavioural Choice Theory is based on decision making and behavioural economic theory which incorporates learning and planning. It attempts to explain how people decide between the behavioural options available to them. For instance, choosing whether to be sedentary or active involves a number of factors such as the availability of sedentary or active alternatives, the perceived benefits and barriers, reinforcement from rewards, both tangible and perceived, and the degree of effort required. To change behaviour the alternative course of action needs to be accessible and enjoyable. For instance, reducing sitting by standing while having a coffee break at work with friends would be more accessible and perhaps appealing to some than standing doing the ironing whilst watching television. The key is identifying behaviours which appeal to the individual.

Table 5.2. Overview of the psychological theories underpinning the STAND structured education course

Theory	Key elements	How they will be applied in the STAND programme
Social Cognitive Theory	<p>Behaviour is driven by goals Behavioural change is influenced by</p> <ul style="list-style-type: none"> • Self-efficacy • Outcome expectations • Barriers to change • Self-regulation <p>Distinguishes between long term and short term goals</p>	<p>Group interaction will facilitate learning through direct experiences (mastery of experiences) and indirect (vicarious) experiences which will enhance self-efficacy Participants will be encouraged to set realistic outcomes and identify the barriers to change A sedentary time self-monitoring tool will be available to facilitate self-regulation and short and long term personalised goals will be encouraged</p>
Implementation intentions	<p>Environmental cues associated with behaviour change reduce the conscious and cognitive effort required to self regulate behaviour and achieve goals</p>	<p>Educators will facilitate group members to develop if “X then Y” examples to reduce sedentary behaviour. For instance, “if the telephone rings, stand up”</p>
Common Sense Model	<p>Threats are conceptualised according to 5 domains:</p> <ul style="list-style-type: none"> • Identity • Cause • Timeline • Consequence • Curability/controllability 	<p>The beliefs relating to each domain will be elicited Diabetes educators will tackle each area to avoid the individual acquiring this important information from alternative sources or developing inaccurate beliefs which could negatively impact on future coping mechanisms</p>
Dual Processing Theory	<p>Information is processed systematically or heuristically depending on the amount of motivation and cognitive effort Systematic processing leads to more robust and enduring beliefs</p>	<p>Promote systematic processing by encouraging active learning – encourage independent thought and encourage questions The educator will adapt an interactive approach and ask open questions to elicit information</p>
Behavioural Choice Theory	<p>Behavioural choices result from the accessibility of the behaviour its reinforcement value</p>	<p>Sedentary behaviour is easily accessible and provides positive reinforcement. The educator will need to guide the group towards identifying less sedentary pursuits which are available and rewarding in addition to highlighting the hazards of excess sedentary time</p>

Curriculum development and feasibility (Phases 1 & 2)

Phase 1: Qualitative data collection and analysis

Semi-structured interviews were conducted to inform the development of the STAND programme. These were performed by a M.Sc. student from Loughborough University with analysis by the student and qualitative researchers from Loughborough University. They explored the views and perceptions of T2DM, awareness and acceptability of reducing sedentary behaviour and opinions about educational interventions with 14 young overweight or obese young adults aged 18-40 years with at least one risk factor for T2DM. This group were representative of the sample to be recruited for the main STAND trial. I used the findings from the work of the M.Sc. student to inform the development of the intervention. The main findings and a description of how these were incorporated in the study are presented in Table 5.3.

Table 5.3. Qualitative study findings.

A description of how these were incorporated in the development of the STAND written curriculum and which psychological theories are relevant to each finding.

Findings from the qualitative study	How this was incorporated in the STAND structured education course	Psychological theory
Limited knowledge of T2DM and its risk factors	An interactive session, using visual aids to discuss what T2DM is, why it occurs and what the main risk factors are	Common sense model Dual processing theory
T2DM happens later in life, little personal meaning. Did not feel they were at risk of T2DM	Present individuals with an indication of their personal T2DM risk which visually display personalised blood, anthropometric and sedentary time feedback with the aim of giving T2DM personal meaning	Common sense model Dual processing theory
Reducing sedentary behaviour was a new concept that they would be willing to try but solutions would need to be personalised	The sedentary behaviour section of the written curriculum would have the greatest time dedicated to it and would allow for open group discussion about the common sedentary behaviours and ways in which individuals could change or substitute behaviours for more appealing alternatives	Social cognitive theory Behavioural choice theory Implementation intentions Dual processing theory
Group based education acceptable but needs to be accessible	Multiple course times and locations were offered to each participant attending subsequent pilot sessions in an attempt to maximise numbers	

Phase 2: Curriculum development

I used these qualitative findings to adapt the PREPARE and DESMOND structured education programmes to target a reduction in sedentary behaviour in young adults. The written curriculum was initially based on the successful PREPARE and DESMOND programmes. I met with members of the study team to discuss desirable content in the STAND structured education programme. I then adapted existing curricula to incorporate the key psychological theories relevant to STAND and to increase the focus on sedentary behaviour. I wrote the STAND curriculum for the pilot sessions. The overview of the pilot curriculum was as outlined below:

- Section A Introduction
- Section B Participant story
- Section C Glucose story
- Section D Consequences and complications of T2DM
- Section E Risk factors for T2DM
- Section F Sedentary Behaviour

To provide ample time for and focus on the discussion of sedentary behaviour, sections of the DESMOND and PREPARE curricula on diet and physical activity were reduced in size. Subsequent alterations to this curriculum and an overview of the curriculum used in the randomised controlled trial are presented later in this chapter. An example of the written curriculum is available in Appendix Four.

Identifying a suitable tool for self-regulation

Self-monitoring is key to the success of behaviour change interventions (Bandura, 1986, Yates et al, 2009). I was responsible for identifying and trialling potential devices to facilitate sedentary behaviour self-monitoring in the STAND intervention. The following criteria needed to be fulfilled by the self-regulation device:

- Objective measure of sedentary time
- User friendly, uncomplicated device
- Sedentary time easily displayed to the individual using the device
- Ability to provide dynamic feedback on changes in sedentary time

The study of sedentary behaviour is still evolving and the only three devices available at the time, which were also commercially available to pilot, were:

- PAM Coach (Move2Health, The Netherlands: www.pam.com),
- ActivPAL (PAL Technologies Ltd., Glasgow, UK: www.paltechnologies.com),
- Gruve (MUVE, Inc., USA: www.muveinc.com/gruve.asp)

PAM device



Figure 5.3. The PAM Coach (Move2Health, The Netherlands: www.pam.com),

The PAM is a waist worn device which measures different levels of activity and converts them into 'PAM points'. This provides an indication of overall activity levels rather than the time spent sedentary. Feedback from personal pilot testing showed that the device was not particularly intuitive to use and importantly, it did not present the amount of time spent sedentary for self-monitoring.

ActivPAL



Figure 5.4. ActivPAL

The ActivPAL (PAL Technologies Ltd., Glasgow, UK, www.paltechnologies.com), is a thigh worn device which determines

posture on the basis of thigh inclination and classifies activity into time spent sitting/lying, standing, or stepping. While the feedback from this device provides a reliable estimate of time spent sitting, using this device would require the participants to regularly initialise their monitor and download their data using expensive specialised equipment and software. Moreover, self-monitoring would be encouraged for as long as the participants wish during the trial. Members of our study team found that wearing the ActivPAL taped to the thigh could be uncomfortable beyond one week. It was concluded that the activPAL was more appropriate as a tool for research rather than personalised self-monitoring for the study participants. Given that the ActivPAL met so many of the desired criteria for a sedentary behaviour monitoring tool, particularly the accurate measurement of the time spent sitting, it was decided to incorporate the ActivPAL into the trial as a secondary outcome measure and also as a means of providing an illustration of sedentary time to the intervention participants when they attended the structured education course. In the educational workshop, personalised data from the ActivPAL were presented to participants. This was achieved by meeting the participants at least one week prior to the workshop to instruct them on how to use the device. The ActivPAL provided data on total sitting time as well as a breakdown of their sitting patterns throughout the day. Long and short-term goals could then be set based on this information, such as targeting less sitting at times of the day where sitting is high and seen to be acceptable to change.

Gruve



Figure 5.5. Gruve

The Gruve device (MUVE, Inc., USA: www.muveinc.com/gruve.asp) is a waist worn accelerometer which monitors sedentary time. The device is connected to a personal computer via a USB and data are downloaded to the interactive Gruve website. This enables the participants to view and track progress on time spent sedentary. This can be viewed on daily, weekly and monthly data charts, allowing the participant to set and revise personal goals. Furthermore, if the participant is sedentary for a prolonged period the device will vibrate to notify them that they have been sedentary and are reaching their 'energy conservation point' (ECP). The ECP marks the point at which the body goes into a reduced caloric burn rate following a prolonged period of sedentary behaviour. The frequency of the vibration will vary across participants and depends on the health information provided to the website by each individual. The vibration function acts as a reminder to stand and move, providing a helpful prompt for behaviour change. One disadvantage of the Gruve device is that the focus of the online feedback is strongly orientated towards calorie expenditure.

Pilot work with four members of the research team and eight study participants provided positive feedback on this device and hence, despite its limitations and in the absence of a commercially available alternative, it was considered the most appropriate self-monitoring device for this study. To overcome the website focus on calorie expenditure, participants would be asked to ignore the calorie information on the site and focus on their sedentary measures. While this situation is far from ideal, in the absence of a suitable alternative device designed specifically for measuring and self regulating sedentary time the Gruve was employed as the self-regulation tool in the STAND RCT.

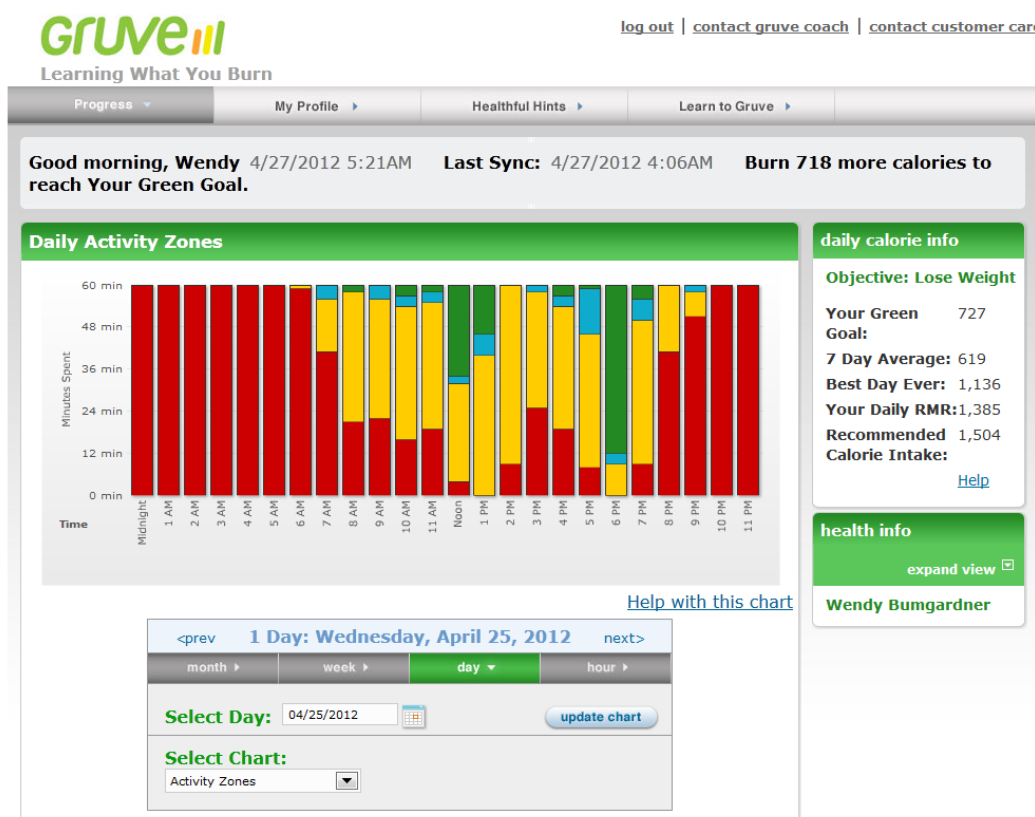


Figure 5.6. Example of the Gruve online feedback. Red bars indicate sedentary time and the total time spent sedentary can be easily calculated or viewed.

A written curriculum, incorporating the ActivPAL feedback and instructions on how to use the Gruve device, was developed for the pilot sessions.

Piloting and subsequent modifications

Aims of the pilot sessions

The pilot sessions of the STAND education workshops had 3 main aims:

- 1) To assess whether the content was relevant and of interest to the target population
- 2) To ensure the correct messages were being conveyed
- 3) To check that the visual and written aids were optimal

Permission to pilot the education intervention was received from the local primary care trusts. Ethical approval was also gained for recruitment from the wider community (ethics approval letter available in Appendix Five).

Educator training

I was one of two trained educators responsible for delivering the pilot sessions. Both educators underwent a quality controlled 2 day residential DESMOND educator training programme. Both educators also attended a Walking Away structured education course (the national roll out of the successful PREPARE programme). Prior to the pilot sessions commencing, we delivered the workshop to work colleagues to ensure timing and pace of delivery were optimal.

Recruitment

Participants for the pilot sessions were recruited from both the community and local general practices. Participants recruited through the community responded to emails or posters about the study. Participants recruited from the GP were identified by a search of GP database for those meeting the inclusion criteria followed by an invitation letter from their GP. To ensure participants would reflect the population recruited for the main randomised controlled trial, the same inclusion and exclusion criteria were applied:

Inclusion criteria

a) Age 18-40 years with a BMI in the obese range ($\geq 30\text{kg/m}^2$; $\geq 27.5\text{kg/m}^2$ for South Asians)

b) Age 18-40 years with a BMI in the overweight range ($\geq 25\text{kg/m}^2$; $\geq 23\text{kg/m}^2$ for South Asians) and with one or more additional risk factor for T2DM from:

- family history of T2DM or CVD in a first degree relative;
- previous gestational diabetes;
- polycystic ovarian syndrome;
- HbA1c $\geq 5.8\%$ (from our local Addition Leicester diabetes screening data a cut off HbA1c of 5.8% provided the best sensitivity and specificity for a diagnosis of prediabetes).
- Impaired glucose regulation (defined according to the World Health Organisation).

Exclusion criteria

Significant illness, steroid use, diabetes, pregnancy or an inability to communicate in English.

Delivery of the pilot sessions

Each pilot structured education course was delivered by myself and one other educator over one 3-hour session at a location and time convenient for the participants. The evening tended to be the most convenient time for the majority of participants. Each pilot session was observed by a researcher trained in delivering DESMOND education sessions and/or qualitative research methodology. The course observer recorded personal observations and conducted semi-structured interviews with participants at the end of the session. Participants also completed feedback forms (Appendix Four). The development of the workshop was an iterative process involving pilot work, feedback, revision and further pilot work in line with the MRC framework for complex interventions.

Pilot results

Three pilot sessions were delivered to 11 participants (4 male, 1 minority ethnic background, age range 18-40 years). Two sessions were delivered to participants recruited through advertising materials distributed in the university town of Loughborough, UK, and one session to participants recruited from a general practice (GP) in nearby Castle Donnington. All pilot sessions were run in the evening at Loughborough University, which was a

location convenient for all those recruited. Each pilot session was observed by a senior researcher with expertise in this area.

Pilot Feedback

Overall, the pilot education sessions were well received. Participants felt they had greater understanding of T2DM and its risk factors as a result of the course and the visual aids employed. Some participants had suggestions for improvements to the visual aids which were incorporated prior to the start of the RCT. Participants enjoyed estimating their personal sitting time, comparing this with the objective feedback from the ActivPAL device and subsequently discussing how to reduce sitting time. Participants said that they would like more time for goal planning so we ensured that this was built into the programme. Some felt the benefits of exercise had to be more strongly emphasised in addition to the benefits of standing more/sitting less and, again, this feedback was used to modify the education programme.

Modifications made

Experienced educators from the DESMOND collaborative provided training on the modifications required for working with younger adults. Table 5.4 provides a summary of the feedback received from the pilot sessions and the changes made. A more detailed account of the feedback provided is available (Appendix Four). An important finding from the pilot sessions was the difficulty in co-ordinating a group of younger people for an education session. Trying to find mutually convenient times and dates for this busy

population (many had work and/or child care commitments) was difficult, and a future consideration for the logistics of the main randomised controlled trial.

The results of the qualitative data and feedback from the pilot sessions were incorporated into the education programme which was subsequently delivered as part of the STAND randomised controlled trial (Chapter Six, Seven, Eight). An overview of the final curriculum is available in Table 5.5. A sample of the written curriculum and participant resources for the education course are available in Appendix Four.

Table 5.4. Overview of the modifications made to the education course from pilot feedback

Key theme identified from feedback	Solution
Educational content – Well planned, good visual content T2DM: insights into T2DM and its risk factors provided, myths were dismissed and key messages were conveyed Some wanted information communicated in a positive light (benefits reducing sitting vs harms excess sitting) They enjoyed discussing ways to reduce sitting	More emphasis was placed on the benefits of reducing sitting Stress importance of existing PA/healthy eating guidance and additional un-quantified benefits of reducing sitting
Visual aids – Good overall but images mostly male Risk analogy– some disliked it, felt it was too contrived	Add more female images Other study teams have used the analogy to good effect - continue
Educators – Helpful	Continue
Timing – Evening/afternoon best	Continue
Length of course– Positive feedback	Continue
ActivPAL – Activity feedback was identified as one of the best bits of the course, they enjoyed estimating how much they sat and comparing it with an objective measure Some download problems	Continue to use the ActivPAL Company contacted for solutions prior to the RCT commencing
Goal setting – Some wanted a specific goal Some wanted more time for goal setting Some wanted the educators to suggest ways to reduce sitting	Need personalised goals but can be more directive if required More time created for goal setting In line with a systematic rather than heuristic processing model, the participants should identify ways to change their behaviour

Table 5.5. Outline of the STAND structured education course which was delivered to the participants in the intervention arm.

Module name	Main aims and educator activities	Theory	Time
<i>Participant story</i>	Participants given opportunities to share their knowledge and perceptions of T2DM risk and highlight any concerns they may want addressed in the programme.	Common Sense Model	8% (15 mins)
<i>Professional story: Glucose story Consequences & Complications Risk factors</i>	Simple non-technical language, analogies, visual aids and open questions used to provide participants with an overview of healthy glucose metabolism, the aetiology, risk factors and complications associated with T2DM. Individual feedback provided on biochemical and anthropometric measures measured at baseline visit. Participants encouraged to assess their personal T2DM risk and identify their modifiable risk factors.	Common Sense Model Dual Process Theory	33% (60 mins)
<i>Sedentary behaviour</i>	Simple non-technical language, analogies, visual aids and open questions used to help participants identify the health hazards associated with excess sedentary time and discuss how reducing sedentary behaviour may reduce future risk of developing T2DM. Participants provided with printed feedback on their sitting time from the ActivPAL. Participants discussed options for reducing sedentary behaviours in everyday life; identified barriers to reducing sedentary behaviour and formed action plans and set personal goals. Practical demonstration of how to use the Gruve device for the self-regulation of sedentary time.	Social Cognitive Theory Implementation Intentions Behavioural Choice Theory	58% (105 mins)

Conclusion

Project STAND phases 1 and 2 led to the development of a specific, evidence-based group structured education programme underpinned by robust psychological theory and tested on its target audience inline with the MRC framework for complex interventions. In phases 1 and 2, I wrote the STAND structured education curriculum, delivered the pilot sessions and made subsequent modifications to the curriculum. I also identified self-monitoring tools capable of sedentary time self-regulation. The STAND randomised controlled trial is the first UK trial, to our knowledge, to address sedentary behaviour change in a population of young adults at risk of T2DM. The methodology for the randomised controlled trial is described in the Chapter Six and the baseline and 3 month results are reported in Chapters Seven and Eight respectively.

Chapter Six: STAND randomised controlled trial: methods and design

Randomised Controlled Trial to Reduce Sedentary Time in Adults at Risk of Type 2 Diabetes Mellitus: Project STAND (Sedentary Time ANd Diabetes)

Chapter overview

This chapter describes the design and methods used to deliver the STAND randomised controlled trial. The overall rationale and hypotheses of the STAND programme of work were described in Chapter Five. The specific aims and design of the STAND randomised controlled trial are outlined below. This is followed by the methodology employed including inclusion and exclusion criteria, recruitment, delivery of the intervention, the measurement of primary and secondary outcomes and the statistical analysis undertaken.

Aims

The STAND RCT aims to assess whether the STAND evidence based structured education programme, combined with a self-monitoring tool (Gruve), can successfully lead to a reduction in sedentary time in young adults at risk of T2DM.

Design

The STAND study is a single centre 2 arm parallel 12 month follow-up RCT designed to assess the effectiveness of a 3 hour group structured education intervention to reduce sedentary time in young adults at risk of T2DM.

Study population

Young adults at risk of developing T2DM were recruited from across Leicestershire and the South East Midlands Diabetes research network.

Inclusion criteria

a) Age 18-40 years with a BMI in the obese range ($\geq 30\text{kg/m}^2$; $\geq 27.5\text{kg/m}^2$ for South Asians)

b) Age 18-40 years with a BMI in the overweight range ($\geq 25\text{kg/m}^2$; $\geq 23\text{kg/m}^2$ for South Asians) and with one or more additional risk factor for T2DM from:

- family history of diabetes or CVD in a first degree relative;
- previous gestational diabetes;
- polycystic ovarian syndrome;
- HbA1c $\geq 5.8\%$ (from our local Addition Leicester diabetes screening data a cut off HbA1c of 5.8% provided the best sensitivity and specificity for those at high risk of diabetes (Mostafa et al. 2010).
- Impaired glucose regulation (World Health Organisation, 2006).

Exclusion criteria

Significant illness, steroid use, diabetes, pregnancy or an inability to communicate in English.

Recruitment

Participants were primarily recruited from primary care in Leicester and Kettering, areas in England with a diverse ethnic and socio-economic makeup. Recruitment was co-ordinated via the East Midland and South Yorkshire Primary Care Research Network (PCRN). The PCRN sent study information to GP practices. Interested practices had the opportunity to meet with the study team to discuss the study in more detail if required. If the practice was agreeable to participation, an electronic GP database search was conducted at the practice to identify participants who met the inclusion criteria. Study invitations were sent by the GP to the participants who then replied directly to the study team. It was anticipated that obese and overweight 18-40 year olds would be a hard to reach group and as such participants were provided with £20 for each clinic visit in addition to reimbursement for travel expenses.

Intervention and control groups

Randomisation

Randomisation (stratified by age, sex, and ethnicity) was set up by an independent statistician using a computer generated block design with stratification by age, sex and ethnicity. The researcher who oversaw the randomisation process was based in a location remote to the study centre (Loughborough University) and had no involvement in the design or delivery of the STAND RCT.

Participants attended the baseline study visit. Once data collection was complete (accelerometer and ActivPAL returned via post 10 days after baseline study visit) the participants were randomised to either the control or intervention group. Participants randomised to the control group received an information leaflet focusing on key illness perceptions of being at risk of T2DM, the importance of increasing physical activity and decreasing sedentary behaviour (Appendix Five). Each individual in the intervention group was invited to attend the STAND structured self-management education programme delivered by trained educators, as described in Chapter Five. All participants and their respective GPs received a letter detailing the results of the blood tests and anthropometric data collected during the study (Appendix Five).

STAND intervention

The intervention was a 3 hour interactive group structured education programme delivered by trained and quality assured educators (see Chapter Five for further detail and Table 5.5 for overview of the curriculum). A range of potential dates, times and locations for the group structured education intervention were offered to those in the intervention group in an attempt to maximise attendance. The structured education programme was delivered by two educators from a potential pool of six who had all been through the residential Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) nationally approved training programme in addition to training to deliver the STAND structured education programme. Educator training was overseen by the DESMOND collaborative. During the education

programme, intervention group participants received detailed feedback on their biochemical and anthropometric outcomes as well as a printed download of their sedentary time as measured by the ActivPAL device (see Chapter Six for details). Instructions on how to use the Gruve device (MUVE, Inc., USA: www.muveinc.com/gruve.asp) sedentary behaviour self-monitoring tool were incorporated in the STAND written curriculum. Participants were provided with a Gruve device and instructions on how to use its main features (see Chapter Six for details).

Intervention group six week follow up

Intervention group participants were telephoned at 6 weeks to ascertain whether they had downloaded the Gruve software, whether they had worn the device and whether they had viewed the internet based feedback. They were also asked whether they had attempted to reduce their sedentary behaviour.

Sample size

The primary outcome was a reduction in sedentary behaviour, measured by an accelerometer at 12 months. The minimum reduction in sedentary behaviour which would yield beneficial metabolic effects has not been determined. Cross-sectional data suggested that a 10% increase in sedentary time was associated with a 3.1cm increase in waist circumference, and that sedentary time was positively associated with clustered metabolic risk (Healy et al. 2008). Using the same dataset, the mean sedentary time was 56.7 hours/week. The minimum clinically important difference would be

5.67 hours/week, reducing to 51.03 (SD 12.1). Sample size was estimated as $2N = (4(Z_{\alpha} + Z_{\beta})^2 s^2) / d^2$ (where d was the true between-arms difference, b was the type II error rate, and α was the type I error rate). Alpha was set at $P = 0.05$ ($Z_{\alpha} = 1.96$) and power at 80% ($b = 0.20$, $Z_{\beta} = 0.842$). This resulted in a required N of 72 in each arm. Incorporating a dropout rate of 25% gives a final N of 89 per arm.

Data analysis

Normality was assessed using the Kolmogorov-Smirnov test, histograms and normal Q-Q plot. Descriptive statistics (mean values and frequencies) were calculated. Continuous data were expressed as mean (standard deviation (SD)) if they were normally distributed. Non-parametric continuous variables were expressed as median (25th and 75th interquartile range (IQR)). Categorical data were expressed as a percentage. Chi square was used to compare categorical variables between two groups. All individuals included in the 3 month analysis presented in Chapter Eight were analysed in the group to which they were assigned. Between group comparisons of change in measured outcomes were conducted using ANCOVA procedures; baseline measures were included as a covariate. Significance was assessed at the 5% level. Statistical tests were performed using SPSS 18.0 software for Chapter Seven and SPSS 20.0 software for Chapter Eight (Statistical Package for the Social Sciences, Chicago, IL).

Data collection and study outcomes

The study visits took place in the research units within University Hospitals of Leicester and Kettering General Hospital. All primary and secondary outcome measures were recorded at study visits at 0, 3 and 12 months (see Table 6.1). The nurses and health care assistants who collected the study data at these visits were blind to the participant randomisation. The participant journey is described in Figure 6.1.

Table 6.1. Data collected at baseline, 3 and 12 months

Data collected	Baseline	3 months	12 months
History (nurse administered questionnaire)			
Medical history	✓	✓	✓
Drug history	✓	✓	✓
Family history	✓	✓	✓
Social history	✓	✓	✓
Blood tests (collected by nurse)			
Fasting glucose	✓	✓	✓
2 hour glucose	✓	✓	✓
HbA1c	✓	✓	✓
Insulin	✓	✓	✓
C-peptide	✓	✓	✓
Lipid profile	✓	✓	✓
Inflammatory biomarkers	✓	✓	✓
Urea and electrolytes	✓	✓	✓
Liver function tests	✓	✓	✓
Vitamin D	✓	✓	✓
Anthropometric data (measured by nurse)			
Blood pressure	✓	✓	✓
Weight	✓	✓	✓
Body fat %	✓	✓	✓
Waist circumference	✓	✓	✓
Psychological variables (self report)			
International Physical Activity Questionnaire	✓	✓	✓
Brief illness perceptions	✓	✓	✓
Hospital anxiety and depression scale (Zigmond et al. 2006)	✓	✓	✓
Self-efficacy	✓	✓	✓
Fatigue and sleep (Chalder et al 1993, Buysee et al 1989)	✓	✓	✓
Objective sedentary time and physical activity measures - devices worn for 10 days			
Actigraph accelerometer	✓	✓	✓
ActivPAL	✓	✓	✓

Primary Outcome

The primary outcome was a reduction in sedentary behaviour at 12 months, measured objectively using the triaxial Actigraph GT3X accelerometer. These accelerometers were the most extensively validated and accurate on the market, albeit for physical activity assessment, and they are the only commercially available accelerometers to correlate with energy expenditure (Plasqui et al. 2008). However, recent studies have also used this device to assess time in sedentary behaviour, although there is still debate about the exact counts per minute to use as a representation of time in sedentary behaviour (Healy et al. 2011, Matthews et al. 2008). Accelerometers can provide an estimate of the total volume of sedentary behaviour and are also capable of detecting short, incidental breaks in sedentary time (<5 minutes), which may not be feasibly recorded by self-report measures.

Participants were provided with an accelerometer at the end of each study visit. They were requested to wear the accelerometer on their waistband (in the right anterior auxiliary line) for ten consecutive days during waking hours. At the end of the 10 days they were asked to return the accelerometer to the study team in a stamped addressed envelope. The Actigraph was initialised with a start and stop time and a 5 second epoch. Non-wear time was defined as 60 minutes of consecutive zeros on all three axes and days with at least 10 hours wear time were considered valid (Healy et al. 2007, Healy et al 2011, Banloski et al. 2011). Participants with less than 4 days of valid wear time were excluded from the analysis (Trost et al. 2005). The duration

(minutes/day) spent in sedentary, light, moderate, and vigorous physical activities were defined using Freedson cut points (Freedson et al. 1998). The primary outcome measure was sedentary time defined as time <100 counts per minute (Healy et al. 2011). Data were analysed using 15s epochs.

Secondary outcomes

Physical Activity

Physical activity and body posture (sitting, standing, stepping) were measured objectively using the Actigraph and ActivPAL accelerometers as well as through self report using the short International Physical Activity Questionnaire (IPAQ) (Rosenberg et al. 2008). The Actigraph GT3X accelerometer was used to measure steps per day, total body movement (counts per day), and time in light-, moderate- and vigorous-intensity physical activity as determined by counts per minute using cut points proposed by Freedson et al (Freedson et al. 1998). The ActivPAL is a thigh worn accelerometer and inclinometer which measures the angle of the thigh, providing data on participant posture (i.e. sitting or lying vs standing) and time spent in sedentary behaviour (sitting or lying). The activPAL has been shown to be a valid and reliable tool for the assessment of sitting in adults (Grant et al. 2006, Kozey-Keadle et al. 2007, Hart et al. 2011). The ActivPAL was worn on the thigh for the same 10 day period as the accelerometer.

Self-reported physical activity and sitting

Participants completed the short 'last-seven-days' self-administered format of the IPAQ as a self-report measure of physical activity and sitting time. This

questionnaire provides a comprehensive measure of moderate- to vigorous-intensity activities carried out for more than 10 continuous minutes at work, in the home, as transport and during leisure time. (Rosenberg et al. 2008). The IPAQ has been shown to have reasonable validity compared to accelerometer data ($\rho \sim 0.4$) and test-retest reliability ($\rho \sim 0.7$) in the UK when used as a measure of total moderate- to vigorous-intensity physical activity (Craig et al. 2003). The IPAQ sitting question asks “During the last 7 days, how much time did you usually spend sitting on a week day?”. The reliability and validity of the IPAQ sitting question in a sample from four countries were acceptable, with validity tested against accelerometers (Rosenberg et al. 2008).

The Marshall sitting survey was also used to measure sitting time. This uses domain specific questions about sitting time and has been shown to have reasonable validity and reliability (Marshall et al. 2010).

Biochemical variables

Participants were invited to attend each clinical measurement session after a 12-hour fast and 24 hours of avoiding vigorous intensity exercise. Plasma glucose, lipids and liver function tests were all measured using standard enzymatic endpoint methods on an ADVIA Chemistry System (Bayer Healthcare, NY, USA), and the LDL fraction subsequently calculated by the Friedewald formula (1972). Dyslipidaemia was defined as lipid lowering treatment or triglycerides ≥ 1.7 mmol/l or HDL < 1.03 (males) or < 1.29 mmol/l (females) (Alberti et al. 2005) and an abnormal ALT was defined as > 53 iU/L.

HbA1c was measured by ion exchange liquid chromatography (G7; Tosoh, Tokyo, Japan). Plasma insulin and C-peptide concentration were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Mercodia, Uppsala, Sweden). Vitamin D (25-Hydroxyvitamin D) was quantified using liquid chromatography mass spectrometry (6410 Triple Quad, Agilent Technologies UK Ltd, Wokingham, UK) and deficiency was defined as <30nmol/l. Serum was collected and frozen for subsequent analysis of inflammatory bio-markers (hsCRP, TNF alpha, sIL-6, and sIL-6R) and stored until complete sample sets were collected for a participant to avoid any intra-assay variation. Plasma IL-6, sIL-6R and CRP were determined via non-commercial sandwich ELISAs. Commercially available ELISA kits were used to determine plasma adiponectin, high sensitivity (hs)-TNF- α and hs-IL-10 (R&D systems, Minneapolis, MN).

Anthropometric, demographic and psychological data

Arterial blood pressure was measured in the sitting position (Omron, Healthcare, Henfield, UK); three measurements were obtained and the average of the last two measurements were used. Hypertension was defined as a systolic blood pressure ≥ 140 or diastolic ≥ 90 mmHg or treatment for hypertension (Mancia et al. 2007). Other measures included body weight and body fat percentage (Tanita BC 420SMA, Tanita, West Drayton, UK), waist circumference (midpoint between the lower costal margin and iliac crest), and height to the nearest 0.1 kg, 0.5% and 0.5 cm respectively. Information on current smoking status, medical and medication history, family history and

ethnicity were obtained using a nurse administered questionnaire. The nurses were blind to which arm the participants had been randomised to.

Psychological outcomes

Several important psychological variables were measured. Data collected included quality of life and illness perceptions using the Brief Illness Perceptions Questionnaire (Kind 1998), self-efficacy (Keller et al. 1999), fatigue and sleep (Chalder et al. 1993, Buysse et al. 1989), and anxiety and depression using the Hospital Anxiety and Depression Scale (Zigmond et al. 2006).

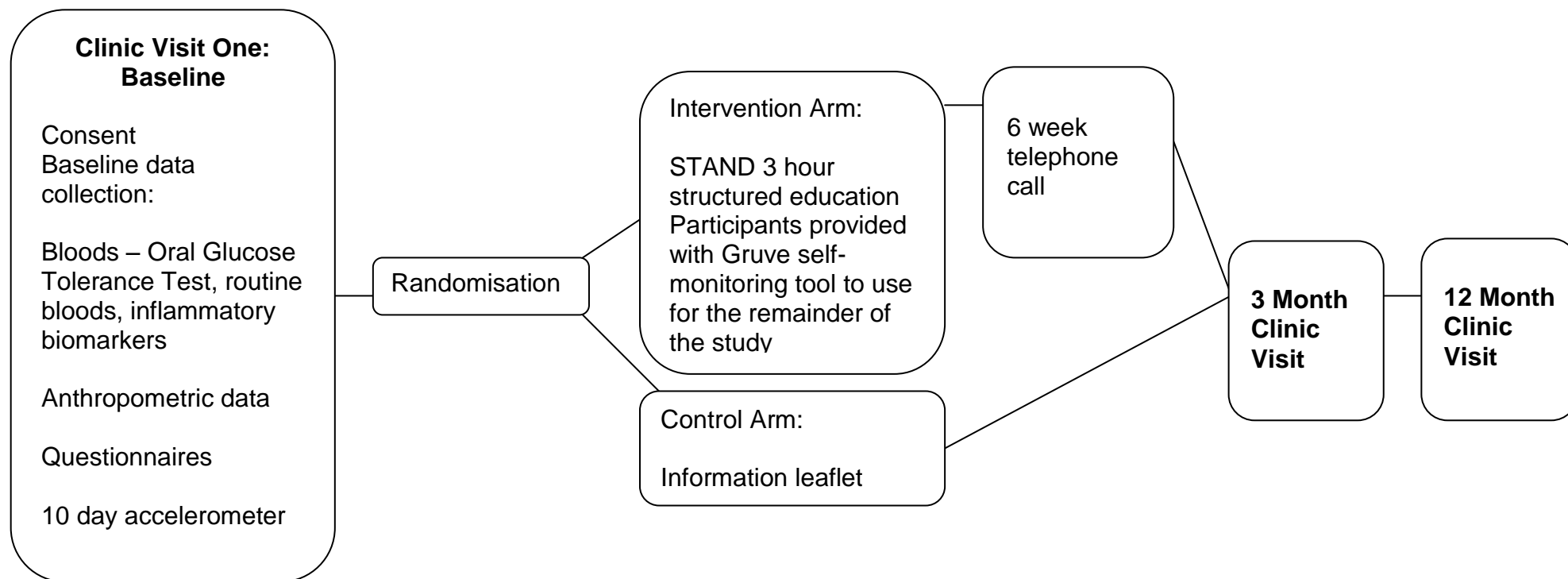
Intervention arm 6 week progress review

The intervention arm experienced a one off education intervention (STAND structured education) followed by one review. Six weeks after the educational workshop, participants in the intervention arm were contacted by telephone to review progress, discuss goal setting and barriers with the aim of supporting behaviour change maintenance. The usefulness of the Gruve device for self-monitoring was also discussed.

Concluding remarks

This chapter presents the methods used to deliver the STAND randomised controlled trial. Chapter Seven and Eight, which follow, describe the baseline data and the 3 month follow-up data.

Figure 6.1. RCT Flow Chart



Chapter Seven: Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from the STAND programme of research

Chapter Overview

In Chapter Two, I highlighted the lack of research available on the prevalence of both diagnosed and undiagnosed T2DM in younger adults aged 18-40 years. As described in Chapter Six, the STAND programme of research involves performing oral glucose tolerance tests (OGTT) and HbA1c on a cohort of young adults with risk factors for T2DM. The data collected at the baseline STAND visit presents a unique opportunity to describe the prevalence of abnormal glucose metabolism in this high risk, under studied population. Furthermore, the data will provide insight into the adequacy of national guidance on screening for T2DM in younger people.

Abstract

Aims: Rising rates of obesity have led to an increasing prevalence of T2DM in young people. Uncertainty exists over the utility of screening younger adults for T2DM as existing datasets have focused on mature (>40 years) cohorts. The aim of this chapter is to determine the prevalence of impaired glucose metabolism in the higher risk younger adults attending the STAND baseline study visit.

Methods: Overweight (with an additional risk factor) or obese adults (18-40 years) were recruited for the Sedentary Time And Diabetes (STAND) randomised controlled trial. Measures included an oral glucose tolerance test (OGTT), HbA1c, biochemical and anthropometric data.

Results: 193 individuals (68% female; median age 33.8 years; median BMI 33.9 kg/m²) were recruited. 43% had a first degree family history of T2DM. Previously undiagnosed T2DM was present in 4.7% (n=9). 18.1% (n=35) had impaired glucose metabolism comprising: 4.7% (n=9) HbA1c \geq 48mmol/mol (6.5%); 9.3% (n=18) HbA1c 42-46mmol/mol (6.0-6.4%); 3.1% (n=6) T2DM on OGTT; 6.2% (n=12) isolated impaired glucose tolerance (IGT); 2.1% (n=4) isolated impaired fasting glucose (IFG); 1% (n=2) both IFG and IGT. 58.5% (n=113) had dyslipidaemia, 28.0% (n=54) had hypertension, 31.1% (n=60) were vitamin D deficient and 7.3% (n=14) had abnormal liver function.

Conclusions: The STAND baseline visit led to the identification of a high prevalence of T2DM and impaired glucose regulation in overweight and obese younger adults. These findings require confirmation in a larger, representative, population.

Trial registration number: Current controlled trials ISRCTN08434554, MRC project 91409.

Background

The appeal and availability of sedentary pursuits and energy dense foods, alongside lower levels of occupational and other physical activities, has culminated in a worldwide obesity epidemic across all age ranges. This change has driven a dramatic shift in the traditional profile of chronic disease, and we now increasingly witness the development of T2DM in young people (Wilmot et al. 2010). The diagnosis of T2DM at a young age has profound implications for both the individual and society, as highlighted in Chapter Two. T2DM is asymptomatic in the initial stages resulting in many developing irreversible complications, often before therapy has even begun. At diagnosis, approximately half of younger adults with T2DM have hyperlipidaemia and/or hypertension and one in five has microalbuminuria (Eppens et al. 2006, Zdravkovic et al. 2004, Upchurch et al. 2003). This accelerated development of micro and macro-vascular complications has serious repercussions. For instance, those diagnosed <45 years of age have a 14-fold increase in the risk of myocardial infarction compared to those without T2DM; in comparison to a 4-fold increase in risk compared to those who had T2DM diagnosed >45 years (Hillier et al. 2003). In addition, early onset T2DM is associated with co-morbidities such as fatty liver disease and obesity, independent risk factors for mortality (Feldstein et al. 2009). T2DM in the young is a relatively recent phenomenon with limited long term follow-up data but it is likely that it will culminate in excess morbidity and mortality.

The early detection and management of T2DM has the potential to reduce the impact of the disease. There is a legacy effect associated with early glycaemic control and even a modest delay in the diagnosis can have negative long term implications (Holman et al. 2008). Identifying people at high risk of T2DM presents an opportunity to intervene and prevent the development of T2DM. There is now a wealth of evidence from studies of older adults which illustrate that progression to T2DM can be prevented or delayed with lifestyle changes which include increased physical activity and dietary modification (Gillies et al. 2007, Yates et al. 2007, Carter et al. 2010).

The importance of the early detection of T2DM in younger people has been acknowledged in the recent publication by NICE guidance which recommends screening high risk individuals aged 25-39 years of age (NICE, 2012). Here, high risk includes black and minority ethnic groups (BME) and people with conditions that increase the risk of T2DM. However, previous T2DM screening studies have predominantly focused on older adults, overlooking the potential disease burden in those younger than 40 years and the evidence base for this recommendation is currently lacking. I therefore investigated the prevalence of impaired glucose metabolism (IGM), T2DM and cardiovascular risk factors in the STAND multi-ethnic cohort of younger UK adults who were obese or overweight with at least one additional risk factor for the development of T2DM.

Methods

Study population and recruitment

In 2011, 193 young adults aged 18-40 years were recruited from across Leicestershire and Northamptonshire, UK as part of Project STAND, a 2-arm parallel group randomised controlled trial. The methodology for this trial was described in detail in Chapters Five and Six . The study was granted ethical approval by the local Research Ethics Committee. Informed verbal and written consent was obtained from all participants. Inclusion criteria were age 18-40 years with a BMI in the obese ($\geq 30\text{kg/m}^2$; $\geq 27.5\text{kg/m}^2$ for South Asians) or overweight range ($\geq 25\text{kg/m}^2$; $\geq 23\text{kg/m}^2$ for South Asians) plus an additional risk factor for T2DM (see Chapter Six for more detail). Recruitment was co-ordinated via the East Midlands and South Yorkshire Primary Care Research Network. An electronic general practice (GP) database search was conducted to identify participants who met the inclusion criteria. Invitations were sent by the GP to the participants who then replied directly to the study team.

Glycaemia

Participants were invited to attend a baseline measurement session after a 12-hour fast and 24 hours of avoiding vigorous intensity exercise. Individuals underwent a standardized 75g OGTT and an HbA1c to measure glycaemia. HbA1c was interpreted according to the 2011 WHO criteria (HbA1c $\geq 48\text{mmol/mol}$ (6.5%) diabetes; 42-46 mmol/mol (6.0-6.4%) “high risk”) (WHO, 2011, National Health Service Check, 2009). The OGTT results were interpreted according to the 1999 WHO criteria and divided into diabetes, isolated impaired fasting glycaemia (IFG), isolated impaired glucose tolerance (IGT) or impaired glucose regulation (IGR) (both

IFG and IGT) (Alberti et al. 1998). In this chapter, diabetes is defined by an OGTT and/or HbA1c result in the diabetes range. Impaired glucose metabolism (IGM) refers to any previously undiagnosed glucose abnormality including an HbA1c \geq 42mmol/l (6%) and/or OGTT defined IFG, IGT or T2DM.

Anthropometric data, laboratory outcomes and statistical methods

A detailed description of the methods employed can be found in Chapter Six.

Results

Of 5056 participants invited by letter to take part in the study, 316 (6.3%) responded, of which 193 were eligible and consented to participate in the study. All 193 participants who completed the STAND study baseline visit were included in this analysis. 68% (n=131) were female. 21% (n=40) were of BME origin (Asian n=23; Black n=10; mixed ethnic origin n=7). Median (+/-interquartile range) age and BMI were 33.8 (29.3-37.9) years and 33.9 (31.2-37.6) kg/m² respectively. 43% had a first degree family history of T2DM. Baseline anthropometric and laboratory data are described in Table 7.1.

Prevalence of impaired glucose metabolism

T2DM was present in 4.7% (n=9) of the study population. IGM was present in 18.1% (n=35). Of those with IGM, 4.7% (n=9) had an HbA1c \geq 48mmol/mol (6.5%)); 9.3% (n=18) HbA1c 42-46mmol/mol (6.0-6.4%); 3.1% (n=6) T2DM on OGTT; 6.2% (n=12) isolated IGT; 2.1% (n=4) isolated IFG; 1% (n=2) both IFG and IGT. 32.5% (n=13) of the BME population had IGM compared to 14.5% (n=22) of the White Caucasian

population ($p=0.01$). 15.3% ($n=20$) of females had IGM compared to 24.2% ($n=15$) males ($p=0.13$). All participants aged <25 years ($n=22$) had normal glucose status.

Cardiometabolic risk

58.5% ($n=113$) had dyslipidaemia and 28.0% ($n=54$) had hypertension. 0.5% ($n=1$) and 4.7% ($n=9$) were prescribed lipid lowering and anti-hypertensive therapy respectively. 7.3% ($n=14$) had an elevated alanine transferase, a marker of possible fatty liver disease. 31.1% ($n=60$) were vitamin D deficient ($<30\text{nmol/l}$).

Discussion

Screening young overweight and obese adults for T2DM successfully identified T2DM (4.7%) and impaired glucose metabolism (18.1%). The T2DM yield in this cohort was similar to other larger screening studies in older UK populations and adds further support to the recent national recommendation to screen those aged 25-39 years for T2DM (NICE, 2012).

The ADDITION-Leicester population based T2DM screening study, with a mean age 57 years, identified 3.3% of the population with undiagnosed T2DM (Webb et al. 2011). These data were based on OGTT results and are comparable with the OGTT T2DM yield (3.1%) in the younger high risk STAND cohort. Similar figures have been reported in other UK studies in overweight and obese populations >40 years, with reported yields between 1.4% and 5.4% (Goyder et al. 2008, Greaves et al. 2004). However, it is important to highlight that the STAND cohort were a high risk group and not representative of the general Leicester population. In Leicester 23% of the population are obese and 36% of BME origin compared to 89% and 21% of the

STAND study population respectively (South East Public Health Observatory 2012, NHS Leicester Joint Strategic Needs Assessment, 2008). The BME populations were underrepresented in this study, a group which typically has more than double the prevalence of screen detected T2DM (Webb et al. 2011). These factors limit the generalisability of our finding. Nonetheless, the yield obtained highlights that undetected T2DM is prevalent in high risk young cohorts and is worth pursuing. Furthermore, NICE recommend targeted screening towards minority ethnic groups aged 25-39 years, a recommendation supported by our finding of significantly more IGM in the BME group and no impaired glucose regulation in any participants under the age of 25 years. However, the prevalence of IGM (14.5%) and T2DM (2%) in the White Caucasian population was still considerable. The increasing prevalence of abnormal glucose metabolism in younger White Caucasian adults is recognised and requires further exploration in larger studies (Wiegand et al. 2004).

The prevalence of IGM in this younger population has implications for clinical practice. T2DM in younger people represents an aggressive phenotype with multiple co-morbidities (hyperlipidaemia, non alcoholic fatty liver disease, morbid obesity) and the rapid development of complications such as nephropathy and hypertension, often more quickly than people with Type 1 DM and despite relatively tight glycaemic control (Eppens et al. 2006). Early detection of T2DM in this group is paramount in order to prevent the development of irreversible complications during their working lives. This is particularly important in young women of child bearing age. If a woman with undiagnosed T2DM becomes pregnant, there is substantial risk to the unborn foetus, particularly during organogenesis in the first trimester when congenital defects occur in the presence of uncontrolled hyperglycaemia (CEMACH, 2007).

Such risks can be minimised by tight glycaemic control and high dose folic acid in early pregnancy (CEMACH, 2007). In view of the high rates of IGM in our young cohort, it would seem sensible to consider T2DM screening in obese women and overweight women with a family history of diabetes or cardiovascular disease.

The main strengths of this study are the unique insights into the prevalence of dysglycaemia and cardiovascular risk factors in a contemporary younger high risk UK population. However, interpretation of the data requires some caution given the sample size, small in comparison to large T2DM screening studies. Also, these participants were motivated subjects who volunteered for inclusion in a randomised controlled behavioural intervention trial on the basis of being 'at risk', and this may limit how generalisable the findings are. However, few data are available on the prevalence of impaired glucose metabolism in this group so the findings of this study fill a gap in current knowledge.

In conclusion, screening for T2DM in a high risk multi-ethnic population of younger adults successfully identifies T2DM and IGM. The findings will need confirmation in larger populations.

Table 7.1. Anthropometric and laboratory outcomes

Descriptive (n=187-193)	n=	Median/% (IQR)	95% CI
Age (years)	193	33.8 (29.3-37.9)	32.1-33.7
Gender (% female)	193	67.9	
Ethnicity (% BME)	193	20.7	
Hypertension (%)	193	28.0	
Systolic BP (mmHg)	193	119 (112-129)	119.1-123.2
Diastolic BP (mmHg)	193	83 (78-89)	82.7-85.5
BMI (kg/m ²)	193	33.9 (31.2-37.6)	33.9-35.3
Obese, BMI ≥30kg/m ² (%)	193	88.6	
Waist (cm)	193	101 (94-111)	102-105
Waist Hip Ratio	193	0.88 (0.81-0.95)	0.87-0.90
Body fat (%)	193	41.9 (35.2-46.2)	39.6-41.6
Fat free mass (%)	193	53.9 (49.4-66.3)	55.7-59.4
Hyperlipidaemia (%)	193	58.5	
Cholesterol (mmol/l)	192	4.8 (4.2-4.8)	4.8-5.1
LDL (mmol/l)	188	3.0 (2.4-3.4)	2.9-3.1
HDL (mmol/l)	191	1.2 (1.0-1.4)	1.2-1.3
Trig (mmol/l)	192	1.3 (0.9-1.9)	1.4-1.8
HbA1c (mmol/mol)	191	46 (36-40)	38-39
HbA1c (%)	191	5.6 (5.4-5.8)	5.6-5.7
Fasting glucose (mmol/l)	192	4.8 (4.5-5.1)	4.8-5.2
2 hour glucose (mmol/l)	192	5.2 (4.3-6.4)	5.3-6.1
ALT (iu/l)	192	23 (17.34)	26.0-31.2
AST (iu/l)	187	22 (18-29)	23.2-25.7
Vitamin D <30nmol/l (%)	190	31.1	

Results presented as median (interquartile range (IQR)) or percentage (%).

BME = black or minority ethnic group.

Chapter Eight: Sedentary Time ANd Diabetes (STAND): a randomised controlled trial

Chapter Overview

This chapter describes the Sedentary Time ANd Diabetes (STAND) randomised controlled trial (RCT), designed to assess the effectiveness of the STAND group structured education programme to reduce sedentary behaviour in young adults at risk of T2DM. The development of the STAND intervention and a detailed description of the methods employed are available in Chapters Five and Six of this thesis. During the RCT described in this chapter, I was responsible for developing the protocol, study documents, obtaining regional Research Ethics Committee and local Research and Development approval. I led and co-managed the team of researchers working on this trial (Appendix One). I was responsible for managing the logistics of the trial, planning study visits, participant flow and overseeing recruitment. I was a STAND educator and delivered the structured education intervention in the trial, as such data collection was performed by an independent team of researchers. I oversaw the delivery of the RCT from the initial planning stages through to month 3 of recruitment in May 2011. In June 2011 I went on maternity leave and I am extremely grateful to Dr Charlotte Edwardson, who managed STAND study team and trial logistics during this time. On my return from maternity leave, I was responsible for data analysis and interpretation. This chapter reports the 3 month follow-up data and focuses on changes in sedentary behaviour, measured by accelerometer (the primary outcome), in addition to key biomedical outcomes.

Abstract

Background: The rising prevalence of T2DM in younger people is a major public health concern. Sedentary behaviour has been identified as a risk factor for T2DM, independent of physical activity. Project STAND (*Sedentary Time ANd Diabetes*) is a randomised controlled trial which aims to reduce sedentary behaviour in younger adults at high risk of T2DM.

Methods: Overweight and obese individuals aged 18-40 years were recruited from primary care in Leicester and Kettering, UK. Participants were randomly assigned to the intervention or control group. The intervention group received a 3 hour structured education programme designed to reduce sitting time, facilitated by the Gruve device for self-regulation. The primary outcome was a reduction in sedentary behaviour as measured by accelerometer (count <100/min). Secondary outcomes included physical activity, self-reported sitting time, fasting and 2h OGTT, lipids, body weight, waist circumference and blood pressure. Study visits occurred at 0 and 3 months.

Results: A total of 187 individuals (68% female, mean age 32.8yrs) were included. At 3 months the intervention group had reduced their sedentary time by 16.95 minutes per day (-16.95 (-40.80 to 6.90)) compared to baseline. However, the control group also reduced their sedentary time from baseline (-5.86 (-21.95 to 10.24). Overall, the intervention group reduced their sedentary time by 9.7 minutes per day compared with the control group (-9.74 (-34.27 to 14.79), $p=0.43$). The intervention group also demonstrated a significant reduction in fasting glucose (-0.52mmol/l (-0.29 to -0.01), $p=0.031$) in addition to beneficial changes in fasting insulin, systolic blood pressure and body fat % which just failed to reach statistical significance (-

3.07mU/l (-6.24 to 0.11), $p=0.058$; -2.06 mmHg (-4.52 to 0.39), $p=0.099$; -0.54% (-1.11 to 0.29), $p=0.063$ respectively). No significant changes in physical activity, weight or lipids were seen between groups.

Conclusions: The STAND structured education programme did not lead to a significant reduction in sedentary time at 3 months post intervention, but some favourable biomarker changes were observed.

Introduction

The development of T2DM at a young age has profound implications for the individual and society. As highlighted in Chapters Two and Three, the early onset of this condition is associated with the aggressive onset of micro- and macro-vascular complications. There is an urgent need to identify novel approaches to prevent the development of T2DM in younger high risk adults. Previous public health guidance has focused on the promotion of adequate amounts of physical activity for T2DM prevention, for which there is a wealth of convincing data on the benefits (Gillies et al. 2007). However, this approach overlooks the substantial proportion of time individuals spend sedentary (sitting and/or lying down). The average adult spends 50-60% of their time in sedentary pursuits (Healy et al. 2008), not surprising considering so many everyday activities rely on a seated posture (driving, computer, television etc.). There is accumulating evidence that excess sitting increases the risk of dysglycaemia and T2DM (Dunstan et al. 2012, Hu et al. 2003, Wilmot et al. 2011; also see Chapter Four of this thesis). The adverse effects of excess sedentary time on glucose regulation are immediate with demonstrable and significant increases in post prandial glucose excursions (Dunstan et al. 2012). Although recent T2DM

prevention guidance (NICE, 2012) has started to recognise the role of sedentary time, recommending that reducing sedentary time may be beneficial, there are no robust data to illustrate that reducing sedentary time is possible and if it is, what the exact benefits are.

The primary aim of project STAND is to assess whether an evidence based structured education programme, combined with a self-monitoring tool (Gruve), can lead to a reduction in sedentary time in young adults at risk of T2DM. The secondary aim is to assess the cardio-metabolic effects of any change in sedentary time. The outcome of this trial is important. Although excess sedentary time is now recognised as a risk factor for adverse health outcomes, there is a lack of evidence from long term intervention trials to support the hypothesis that reducing sedentary behaviour is possible and/or sustainable and whether such a change in sedentary behaviour is associated with health benefits.

Methods

Design

The methods for the STAND randomised controlled trial have been described in detail in Chapter Six. In brief, project STAND is a 2 arm parallel RCT designed to assess the effectiveness of a 3 hour group structured education intervention to reduce sedentary time in young adults at risk of T2DM. The trial includes follow-up at 3 and 12 months. This chapter reports data from the 3 month follow-up visit.

Data collection and study outcomes

All primary and secondary outcome measures were recorded at study visits at 0 and 3 months. A participant flow diagram is available in Figure 6.1. Data were collected by a nurse and health care assistant who were blind to participant randomisation.

Primary Outcome

The primary outcome was a reduction in sedentary behaviour, measured objectively using the triaxial Actigraph GT3X accelerometer.

Secondary outcomes

Secondary outcomes reported in this chapter focus on the biochemical and anthropometric outcomes in addition to objective and self-reported measures of physical activity and sedentary behaviour.

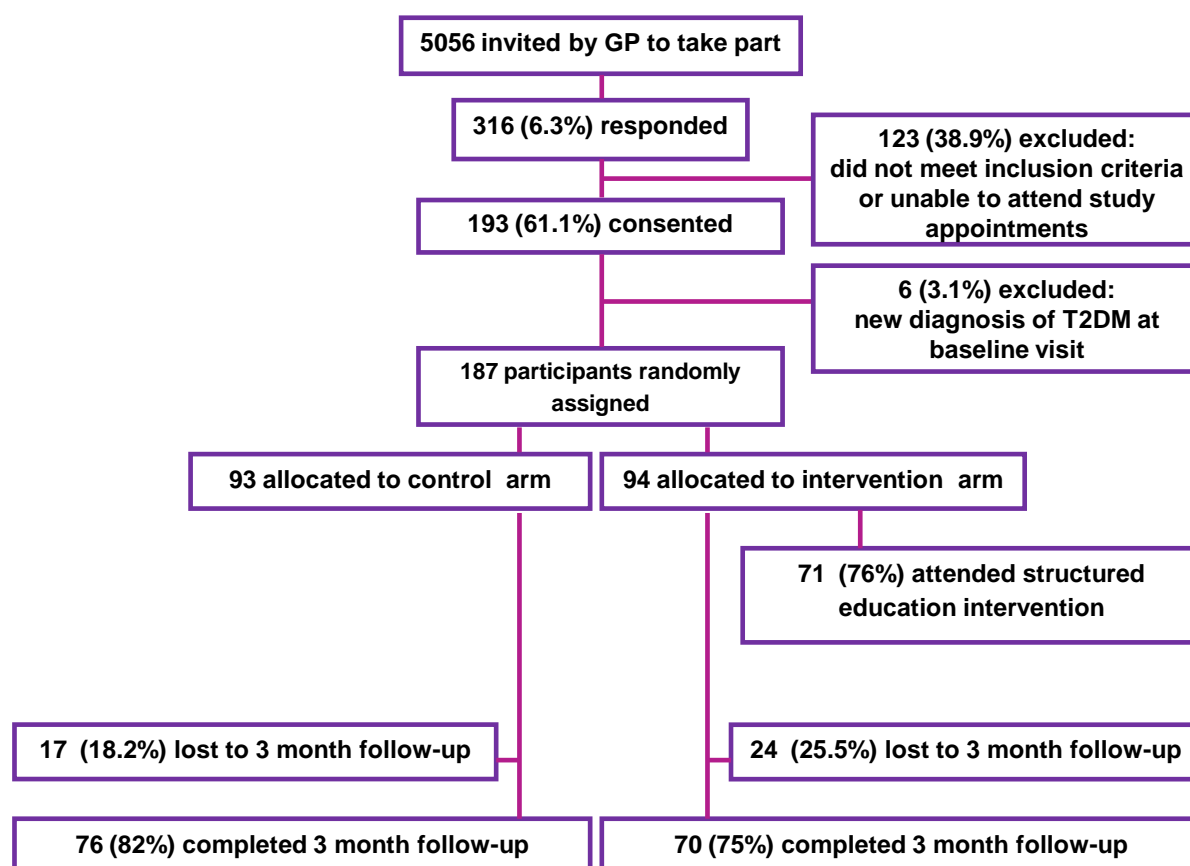
Results

Study cohort

The study enrolment, randomisation and retention at 3 months are shown in Figure 8.1. Of 5056 participants invited by letter to take part in the study, 316 (6.3%) responded, of which 193 were eligible and consented to participate in the study between March 2011 and November 2012. Six participants were diagnosed with T2DM at the baseline study visit and were excluded. Participants (n=187) were randomised to the intervention or control group. 41 (21.9%) participants were lost to follow-up, 17 in the control group and 24 in the intervention group. Baseline

demographic, anthropometric, biochemical and accelerometer characteristics of the participants are displayed in Table 8.1.

Figure 8.1 Enrolment, randomisation and retention of participants.



Intervention

94 participants were randomised to the intervention group. Of these, 71 (76%) attended the STAND structured education intervention. A total of 23 sessions were delivered with an average attendance of 3 participants per session.

Primary outcome

The majority of participants had valid accelerometer data at baseline (151/187, 81%) and two thirds had valid accelerometer data at 3 months (95/146, 65%). Of the 187

randomised participants, 95 (51%) participants had valid accelerometer data from both 0 and 3 month visits which met predefined criteria for analysis. At 3 months the intervention group had reduced their sedentary time by 16.95 minutes per day (-16.95 (-40.80 to 6.90)) compared to baseline. However, the control group also reduced their sedentary time from baseline (-5.86 (-21.95 to 10.24)). There was an overall reduction in sedentary time of 9.74 minutes in the intervention group compared with the control group, which failed to reach significance (-9.7 (-34.3 to 14.8), $p=0.432$) (Table 8.2). The effects of accelerometer wear time on outcomes were examined and adjusting for change in wear time between 0 and 3 months did not influence the results obtained. In addition, a per protocol analysis was performed which did not alter the results obtained.

Physical activity and self-reported sitting time

There were no significant differences in accelerometer derived MVPA, light physical activity, steps or accelerometer counts. There were also no significant differences in self-reported MVPA or sitting time (Table 8.2).

Glucose regulation

Table 8.2 shows changes in measures of glucose, insulin and HbA1c at 3 months. Fasting glucose decreased significantly in the intervention group compared with the control group (-0.51 mmol/l (-0.29 to -0.01), $p=0.031$). There was also a reduction in fasting insulin in the intervention group which approached statistical significance (-3.07 (-6.24 to 0.11), $p=0.058$). There was a decrease in the 2 hour glucose and HbA1c values in both groups, with no significant change between groups ($p=0.61$, $p=0.67$ respectively).

Biochemical and anthropometric outcomes

There was no difference in measured lipids, weight, body mass index or waist circumference between groups. There was a trend towards lower systolic blood pressure (-2.06 (-4.52 to 0.39), $p=0.099$) and body fat % (-0.54 (-1.11 to 0.29), $p=0.063$) in the intervention group.

Adherence

Of those randomised to the intervention group, the majority ($n=71$, 76%) attended the structured education programme. Of those with valid accelerometer data at 0 and 3 months who were included in the final primary outcome analysis (Table 8.2), 37 of 42 (88.1%) intervention participants had attended the structured education programme. Forty-five (48%) intervention group participants were contacted via telephone 6 weeks after attending the structured education programme. All of these participants ($n=45$, 100%) reported that they had tried to reduce their sitting time and that they would recommend the STAND structured education programme to a friend. A qualitative analysis of the data obtained is beyond the scope of this thesis, but the overall impression from participants was that they found the educational programme interesting, informative and felt they had learned how to reduce their personal risk of T2DM. 31 of 45 (69%) had downloaded the Gruve device to their computer (the device cannot be used without initialising online). Of those who performed the download, 19 out of 31 (61%) were still using the Gruve device at the 6 week telephone follow-up, 10 out of 31 (32%) had used it initially but were no longer doing so and 2 out of 31 (9%) had downloaded it but never used it. Of the 29 participants who wore the Gruve device, the majority ($n=26$, 90%) wore it everyday; 22 out of 29

(76%) downloaded their activity levels to the Gruve website and viewed their feedback. Most participants (24 out of 29, 83%) found the vibration function useful but 5 out of 29 (17%) did not.

Discussion

The primary results of this study show that the STAND group structured education programme was not effective at reducing sedentary behaviour in young adults at risk of T2DM. However, the participants in the intervention group did derive some health benefits that may have resulted from the education programme, with a significant reduction in fasting glucose and a trend towards a significant reduction in fasting insulin, systolic blood pressure and body fat percentage. It is not clear what the driver of these changes were but possibilities include changes in sedentary behaviour or physical activity which the measurement tools were not sensitive enough to detect, or changes in diet.

STAND is the first trial to assess structured education to reduce sedentary time in young adults at risk of T2DM. There are examples now emerging of small workplace environmental interventions which have aimed to reduce sedentary time. For instance, a 4 week intervention which employed a sit-stand desk device in sedentary workers resulted in a 66 minute/day (224%) reduction in sitting time, although removal of the device negated all improved observations within 2 weeks (Pronk et al. 2012). In another small study (n=28), an education intervention combined with a 5 day computer software prompt led to a significant reduction in the number and duration of sitting episodes in office workers, but no change in overall sitting time. The computer prompt plus education group had more favourable changes in the

number and duration of sitting events than the education alone group (Evans et al. 2012). Both of these studies, although small in size and duration, highlight the importance of environmental prompts when attempting to reduce sedentary time and this element of the STAND intervention (e.g. the Gruve or possible self change of one's environment) may not have been sufficiently potent.

There are a number of other possible reasons why the STAND intervention group failed to demonstrate a significant reduction in their sedentary time. I will discuss these factors under the subheadings of 'measurement issues', 'methodology issues', 'the STAND intervention' and 'behavioural and environmental issues'.

Measurement issues

The STAND RCT used Actigraph accelerometers to record sedentary time. Although these are the most widely used devices to objectively measure this behaviour, these devices are designed to measure movement and not posture. For instance, a participant who stands (no accelerometer movement detected) is likely to be recorded as being sedentary. It is therefore feasible that a participant who reduced their sitting time by substituting sitting with standing may not have had a detectable reduction in sedentary time on their accelerometer. Furthermore, significant controversy exists regarding the optimal accelerometer cut points used to define sedentary time, the optimal epoch length, the number of days used to define a valid day and the definition of non-wear time. In STAND, less than 100 counts per minute, the commonly used cut point, originally proposed by Freedson (1998), was used. However this cut point is not based on robust data and studies reporting the validity of this cut point in adults are limited (Atkin et al. 2012, Matthews et al. 2008, Kozey-

Keadle et al. 2011). In an attempt to overcome some of the measurement issues highlighted above, we opted for a short epoch length and extended the wear time to 10 days in an attempt to maximise wear time. Despite this, only half of the participants had valid accelerometer data at 0 and 3 months. It may be possible that asking participants to wear the accelerometer for a longer period may lead to reduced compliance. As a result of the above issues, the low number of participants with valid accelerometer data meant that the trial was subsequently underpowered to detect a significant difference in the primary outcomes. Although the sample size calculation allowed for a 25% drop out rate, this did not take into account the difficulties encountered with valid accelerometer data, which, combined with the loss to follow-up (which was 22%), led to a substantial reduction in valid accelerometer data at both 0 and 3 months.

Methodology issues

The study of sedentary behaviour is still in its infancy and this is the first large randomised controlled sedentary behaviour intervention trial in young adults at risk of T2DM. However, selecting this younger, high risk overweight and obese group of participants with higher than average baseline sedentary time may have limited the potential of the intervention. For instance, these participants spent 77% of their time sedentary, far higher than previously reported values of 50-60% of time spent sedentary by older groups of participants (Healy et al. 2008). This may have made behaviour change in our particular group even more challenging. In addition to this, selecting a younger group made coordinating participants so they could attend the group structured education extremely difficult. Given their age, this was a group of with many other factors competing for their time (work, small children etc.) and this

limited the number we were able to assemble for each education session (n=3) which could feasibly have compromised some of the benefits derived from learning in a group setting. The difficulties encountered with engaging this group were further reflected in the higher than average loss to follow-up rates, despite financial incentives to attend study appointments (Davies et al. 2008, Yates et al. 2008). While there is a need for effective novel interventions to prevent T2DM in young people, it might have been advantageous to select an older population for such a preliminary behaviour change study. And then move to the younger adult ranges subsequently.

The STAND intervention

The STAND structured education programme was a complex intervention based on the best available psychological theory and available self-monitoring tools. It was delivered by trained educators with reasonable participant attendance (76%) at the intervention education session, higher in those who had valid accelerometer data at 0 and 3 months who were included in the final analysis (88%). The feedback from the course was positive and 100% of participants surveyed reported attempting to reduce their sitting time. However, the Gruve self-monitoring tool had some limitations, reflected in the fact that only 69% reported using it. This may be related to the lack of immediate visual feedback on the device and the reliance on downloading data to a computer to view any progress made. Furthermore, the website provided participants with the opportunity to record and review their physical activity and dietary intake, if so desired. Although the educators had advised participants to focus on sedentary time, given the desirability of weight loss and the unrelenting messages to aim for a normal body weight from multiple sources (media,

health care professionals, etc) it is possible that the Gruve device may have influenced the results obtained by redirecting participant attention to dietary intake and weight rather than sitting per se, possibly reflected in the non significant trend towards lower body weight, fat percentage, BMI and waist circumference in the intervention group. In the future, small, reliable and user friendly sedentary time self-regulation tools which are designed and fit for purpose will be required to facilitate self-regulation.

Behavioural and environmental issues

Finally, there are behavioural and environmental issues to consider. Sedentary behaviours are ubiquitous and it is possible that the time that these younger participants spent in sedentary pursuits (77%) was devoted to activities simply too desirable (e.g. television watching) or apparently necessary (e.g. sitting at work or driving) to permit significant change. While certain behaviour settings such as screen time, workplace and transportation have been identified as key factors in excess sitting, we do not as yet have a full understanding of the determinants of sedentary behaviour which are likely to operate in distinct ways and in different contexts (Owen et al. 2011). A more detailed understanding of these determinants will hopefully lead to the development of successful sedentary behaviour interventions in the future.

It is possible that in the short term, the intervention group in the STAND study initially reduced their sedentary behaviour but at follow-up at 3 months, this change was not sustained. This reflects the inability to continue to strive for a long term goal with no immediate effect and high personal cost (Gollwitzer et al. 1999). For instance, if an individual starts to exercise regularly they may notice a difference in body shape/size

or well being. The same may not be true of sedentary behaviour and maintaining any change in behaviour without tangible benefits is challenging. Furthermore, Leventhal (1980) proposes in his common sense model that how an individual conceptualises a health threat (T2DM in this case) depends on other sources of information such as lay information, significant others (friends, doctors etc) and previous experience. Feedback during the pilot and RCT education courses suggested that messages about the harms of excess sitting and the potential benefits in reducing sitting time were new. This is not surprising given only 10% of primary care patients receive sedentary behaviour counselling compared to 53% who receive physical activity advice (Shuval et al. 2012). If the message about the benefits of reducing sitting time were not subsequently reinforced by other key sources (doctors, family, friends, media etc) then the impact of the messages conveyed during the STAND programme may have lost importance over time. A full process evaluation of the RCT is beyond the scope of this thesis but this will hopefully shed light on some of the issues raised.

The STAND RCT has raised a number of issues which will need to be considered by researchers in this field. There is a real need to develop valid and reliable accelerometer data (e.g. cut points) to define sedentary behaviour while a more universal approach to accelerometer data analysis will make comparison across studies easier. The ability to self monitor and self regulate behaviour seems key to the success of behavioural interventions (Bandura, 1995). Currently there is no optimal tool which allows for this and the future development of such devices is a priority for future research. Finally, there are a number of potential barriers to reducing sedentary time and further detailed investigation into what these barriers

are and how we can help individuals overcome them will also be key to the success of future sedentary behaviour intervention trials.

Despite no significant change in sedentary time or physical activity, there was a significant reduction in fasting glucose in the STAND intervention group. The exact cause of this fall in fasting glucose is uncertain but possible factors include changes in activity patterns which were not captured by the measurement tools used or changes in diet which were not measured. The change in fasting glucose between groups (-0.51mmol/l) was of a magnitude greater than other lifestyle intervention interventions. For instance, the PREPARE programme, designed to increase walking activity in those with IGT, demonstrated a significant decrease in fasting glucose of -0.32mmol/l compared with the control group (Yates et al. 2009), while The Diabetes Prevention Program showed a significant reduction in fasting glucose of ~0.3mmol/l in both the metformin and lifestyle groups compared with placebo at 6 months (Diabetes Prevention Program, 2002). Lifestyle interventions tend to have a greater impact on glucose in studies with higher baseline BMI (Gillies et al. 2007) and this may have contributed to the substantial reduction in fasting glucose in the STAND cohort.

In conclusion, the STAND structured education programme failed to significantly reduce sedentary behaviour in a group of younger adults at risk of developing T2DM. In the future, short term intervention studies are required to identify and overcome the specific barriers to behavioural change, in addition to the development of validated and reliable methods of objectively measuring and monitoring sedentary time.

Table 8.1. Clinical, demographic and activity characteristics of study participants overall and by group at baseline

	n	Total	n	Control	n	STAND intervention
Number of participants (n)		187		93		94
Age	187	32.8 ± 5.6	93	33.3 ± 5.8	94	32.4 ± 5.5
Female	187	128 (68)	93	62 (67)	94	66 (70)
White ethnic background	186	149 (80)	93	74 (80)	93	75 (80)
Black/ minority ethnic group	186	37 (20)	93	19 (20)	93	18 (19)
1 st degree family history diabetes	187	75 (40)	93	37 (40)	94	38 (40)
Antihypertensive therapy	187	9 (5)	93	4 (4)	94	5 (6)
Statin Therapy	187	1 (1)	93	0 (0)	94	1 (1)
Smoker	187	40 (21)	93	23 (25)	94	17 (18)
BMI (kg/m ²)	187	34.6 ± 4.9	93	34.5 ± 5.0	94	34.6 ± 4.9
Waist circumference (cm)	187	103.3 ± 13.9	93	102.7 ± 14.0	94	103.9 ± 13.8
Body fat (%)	187	40.6 ± 7.1	93	40.5 ± 7.0	94	40.8 ± 7.2
Weight (kg)	187	98.6 ± 18.6	93	98.5 ± 18.2	94	98.7 ± 19.0
Systolic blood pressure (mmHg)	187	120 ± 14	93	122 ± 14	94	119 ± 13
Diastolic blood pressure (mmHg)	187	84 ± 10	93	85 ± 10	94	82 ± 9
Fasting glucose (mmol/l)	186	4.8 ± 0.5	93	4.8 ± 0.5	93	4.8 ± 0.6
2 hour glucose (mmol/l)	186	5.4 ± 1.6	92	5.4 ± 1.4	94	5.4 ± 1.8
Insulin (mU/l)	181	12.2 (7.8, 18.2)	90	11.8 (7.4, 17.1)	91	12.4 (7.8, 19.8)
HbA1c (%)	185	5.6 ± 0.3	92	5.6 ± 0.3	93	5.6 ± 0.4
Total cholesterol (mmol/l)	186	4.9 ± 1.0	92	5.0 ± 1.0	94	4.9 ± 0.9
HDL cholesterol (mmol/l)	185	1.3 ± 0.3	91	1.3 ± 0.3	94	1.2 ± 0.3
Triglycerides (mmol/l)	186	1.3 (0.9, 1.8)	92	1.3 (0.9, 1.7)	94	1.3 (0.9, 1.9)

Table 8.1 (cont)	n	Total	n	Control	n	STAND intervention
Accelerometer						
Time accelerometer worn (hr/day)	151	14.4 ± 1.4	77	14.4 ± 1.2	74	14.4 ± 1.5
Sedentary time (hr/day)	151	11.0 ± 1.4	77	11.1 ± 1.25	74	11.0 ± 1.6
Light physical activity (hr/day)	151	2.5 ± 0.7	77	2.5 ± 0.7	74	2.6 ± 0.8
MVPA (hr/day)	151	0.8 ± 0.4	77	0.8 ± 0.4	74	0.8 ± 0.4
Steps	151	7276 ± 3044	77	7100 ± 2780	74	7458 ± 3119
Total body movement counts	151	274624 ± 110248	77	268636 ± 114963	74	280853 ± 105539
Accelerometer (% at each activity level)						
Sedentary time (%)	151	77	77	77	74	76
Light physical activity (%)	151	18	77	17	74	18
MVPA (%)	151	6	77	6	74	6
Self-reported activity data						
MVPA (hr/day), IPAQ	179	1.3 ± 2.2	88	1.1 1.6	91	1.2 1.9
Sitting (hr/day), IPAQ	149	6.8 ± 3.6	76	7.0 ± 3.8	73	6.6 ± 3.5
Sitting (hr/day), Marshall	175	10.7 ± 11.1	89	10.1 ± 4.0	86	9.1 ± 3.5

Categorical data are n (column percent), parametric continuous data as mean ± SD, and non parametric continuous data as median (interquartile range). Sedentary time = <100 counts/min, light intensity activity 100-1951 counts/min, moderate-to-vigorous (MVPA) activity ≥1952 counts/min.

Table 8.2. Change from baseline and the associated intervention effect for outcomes measured at 3 months

	Control	n	STAND Intervention	n	Adjusted intervention effect (intervention vs control)	p
Accelerometer (average mins/day)						
Sedentary	-5.86 (-21.95 to 10.24)	53	-16.95 (-40.80 to 6.90)	42	-9.74 (-34.27 to 14.79)	0.432
Light	-3.55 (-10.61 to 3.51)	53	-5.54 (-15.30 to 4.22)	42	-0.51 (-11.28 to 10.26)	0.925
Moderate-to-vigorous	3.35 (-1.12 to 7.83)	53	2.58 (-2.76 to 7.93)	42	-0.56 (-7.11 to 6.00)	0.866
Steps	-86 (-509 to 338)	53	-20 (-560 to 520)	42	138 (-464 to 740)	0.649
Total body movement counts	15713 (-4882 to 36309)	53	9048 (-16718 to 34813)	42	-6000 (-37083 to 25082)	0.702
Self-reported activity (hrs/day)						
Sitting, IPAQ	-0.40 (-1.74 to 0.93)	50	0.52 (-1.08 to 2.11)	49	1.02 (-0.51 to 2.54)	0.189
MVPA, IPAQ	-0.08 (-0.48 to 0.32)	65	-0.03 (-0.43 to 0.36)	68	0.07 (-0.41 to 0.54)	0.786
Sitting, Marshall	-0.85 (-1.79 to 0.08)	65	0.13 (-0.67 to 0.93)	58	0.57 (-0.59 to 1.72)	0.331
BMI (kg/m ²)	0.09 (-0.16 to 0.34)	75	-0.02 (-0.27 to 0.24)	70	-0.10 (-0.46 to 0.25)	0.564
Waist circumference (cm)	-0.45 (-1.87 to 0.96)	75	-1.77 (-3.56 to 0.02)	70	-1.18 (-3.35 to 1.00)	0.286
Body fat (%)	0.16 (-0.21 to 0.53)	75	-3.78 (-0.82 to 0.06)	69	-0.54 (-1.11 to 0.29)	0.063
Weight (kg)	0.09 (-0.58 to 0.75)	75	-0.13 (-0.84 to 0.58)	70	-0.216 (-1.18 to 0.75)	0.658
Systolic blood pressure (mmHg)	-2.27 (-4.30 to -0.25)	75	-3.58 (-5.30 to -1.85)	70	-2.06 (-4.52 to 0.39)	0.099
Diastolic blood pressure (mmHg)	-1.29 (-2.94 to 0.37)	75	-1.61 (-2.89 to -0.33)	70	-0.97 (-2.85 to -0.90)	0.307
Fasting glucose (mmol/l)	0.16 (0.06 to 0.27)	76	0.01 (-0.08 to 0.10)	69	-0.51 (-0.29 to -0.01)	0.031
2 hour glucose (mmol/l)	-0.27 (-0.61 to 0.59)	72	-0.43 (-0.81 to -0.04)	64	-0.12 (-0.60 to 0.35)	0.609
Insulin (mU/l)	2.34 (-0.56 to 5.24)	66	-0.72 (-2.40 to 0.95)	64	-3.07 (-6.24-0.11)	0.058
HbA1c (mmol/mol, %)	-0.06 (-0.11 to -0.01)	73	-0.08 (-0.12 to -0.03)	68	-0.01 (-0.08 to 0.05)	0.666
Total cholesterol (mmol/l)	-0.06 (-0.23 to 0.10)	73	0.03 (-0.10 to 0.16)	67	0.05 (-0.14 to 0.24)	0.889
HDL cholesterol (mmol/l)	0.01 (-0.04 to 0.06)	70	-0.12 (-0.06 to 0.24)	67	-0.04 (-0.10 to 0.02)	0.151
Triglycerides (mmol/l)	0.09 (-0.18 to 0.36)	73	0.38 (-0.13 to 0.20)	67	-0.11 (-0.40 to 0.17)	0.430

Data are means (95% CI). All reported intervention effects were adjusted for baseline value. N = number of available datasets after excluding missing or invalid data and extreme outliers.

Chapter Nine: Discussion and future directions

Chapter Overview

Previous chapters of this thesis have highlighted the impact of the diagnosis of T2DM at a younger age, identified sedentary time as a potentially modifiable risk factor for T2DM and described the Sedentary Time ANd Diabetes (STAND) programme, designed to reduce sedentary time in young adults at risk of T2DM. This chapter summarises the main findings reported within this thesis, discusses the implications of these findings and identifies areas for future research. A summary of the main findings, strengths and limitations for each study is presented in Table 9.1.

Table 9.1 Overview of the research in this thesis, the main findings, strengths and limitations				
Chapter	Purpose	Main Findings	Strengths	Limitations
Two	<i>T2DM in young adults literature review</i>	<ul style="list-style-type: none"> • <i>Prevalence increasing</i> • <i>Diagnosis is challenging</i> • <i>Complications are frequent and often more severe than T1DM</i> • <i>Management strategies are not as successful as one would hope</i> 	<ul style="list-style-type: none"> • <i>Comprehensive overview of UK data and beyond</i> • <i>Included both paediatric (<18 years) and adults (18-45 years) data</i> 	<ul style="list-style-type: none"> • <i>Most data observational</i> • <i>Few data from intervention trials</i> • <i>Most data from paediatric population</i>
Three	<i>Expedition study to phenotype younger adults with TDM</i>	<ul style="list-style-type: none"> • <i>T2DM and obese groups had similar adverse cardio-metabolic profiles vs. lean control group</i> • <i>T2DM had diastolic dysfunction on cardiac MRI</i> 	<ul style="list-style-type: none"> • <i>Detailed phenotyping of a unique cohort</i> • <i>The use of state of the art cardiac MRI technology</i> 	<ul style="list-style-type: none"> • <i>Small numbers limit generalisability and interpretation of the findings</i>
Four	<i>Sedentary behaviour systematic review and meta-analysis</i>	<p><i>Excess sedentary time associated with:</i></p> <ul style="list-style-type: none"> • <i>112% ↑ risk of T2DM (RR 2.12, 95% CrI 1.61, 2.78)</i> • <i>147% ↑ risk of cardiovascular events (RR 2.47, 95% CI 1.44, 4.24)</i> • <i>90% ↑ risk of cardiovascular mortality (HR 1.90, 95% CrI 1.36, 2.66)</i> • <i>49% ↑ risk of all-cause mortality (HR 1.49, 95% CrI 1.14, 2.03)</i> 	<ul style="list-style-type: none"> • <i>Conclusions based on a large number of studies and participants from around the world</i> • <i>Any form of sedentary behaviour included</i> • <i>Demonstrates clear associations from available epidemiological data</i> 	<ul style="list-style-type: none"> • <i>All studies used self-reported measures of sedentary time</i> • <i>Most studies included measures of TV/sitting time</i> • <i>Conclusions cannot be used to infer causality</i>

Five/Six	<i>Methodology for project STAND</i>	<ul style="list-style-type: none"> • <i>STAND structured education programme was well received</i> • <i>'Sitting less' was a new message to most</i> • <i>Limited availability of sedentary behaviour self-monitoring tools</i> 	<ul style="list-style-type: none"> • <i>Approach in keeping with MRC framework for complex interventions</i> • <i>Structured education programme based on robust psychological theory</i> 	<ul style="list-style-type: none"> • <i>Lack of optimal sedentary behaviour self-regulation tools</i> • <i>No pilot study to assess feasibility of reducing sedentary time</i>
Seven	<i>STAND baseline prevalence of T2DM and IGM in younger adults at risk of T2DM</i>	<ul style="list-style-type: none"> • <i>Undiagnosed T2DM was present in 4.7% and impaired glucose metabolism in 18.1% of obese and overweight individuals aged 18-40 years with risk factors for T2DM</i> 	<ul style="list-style-type: none"> • <i>Unique data on the prevalence of glucose abnormalities from a high risk, younger UK cohort</i> • <i>Informs current UK T2DM prevention strategies</i> 	<ul style="list-style-type: none"> • <i>Relatively small sample size compared to existing T2DM screening studies</i> • <i>Low response rate 6%</i> • <i>Biased sample</i>
Eight	<i>STAND RCT 3 month results</i>	<ul style="list-style-type: none"> • <i>The STAND programme did not significantly reduce sedentary time in the intervention group at 3 months (-9.74 minutes (-34.27 to 14.79), p=0.43)</i> • <i>In the intervention group there was a significant reduction in fasting glucose (-0.52mmol/l (-0.29 to -0.01), p=0.031)</i> • <i>There was also a trend towards improvements in fasting insulin, systolic blood pressure and body fat % which just failed to reach statistical significance</i> 	<ul style="list-style-type: none"> • <i>First large scale sedentary behaviour intervention</i> • <i>Large sample size compared with previous sedentary behaviour interventions</i> • <i>Targeted multiple forms of sedentary time</i> • <i>Objective measure of sedentary time for primary outcome</i> • <i>Recruitment targets were met</i> 	<ul style="list-style-type: none"> • <i>Primary outcome measure (accelerometer) measures movement intensity, not sitting posture</i> • <i>Universal lack of agreement on accelerometer processing rules</i> • <i>Limited accelerometer data at 0 and 3 months</i> • <i>Suboptimal sedentary behaviour self-regulation tool</i>

Chapter Two: T2DM in the young literature review

Chapter Two of this thesis provides an overview of current insights into the implications of T2DM diagnosed at a younger age (<45 years), with focus on the available UK data. Although there have been previous reviews of T2DM in younger adults, none have highlighted data from the UK and most have discussed the findings from paediatric datasets. The findings in this chapter highlight the expansion of young adults with T2DM in the UK, many of which represent an extreme phenotype, particularly vulnerable to the micro and macro-vascular complications of T2DM. This chapter also discussed the main risk factors and pitfalls in the diagnosis and management of this cohort. On the whole, little data is available from the UK. There is a need for robust UK data collection to describe this cohort of high risk individuals, which may in turn facilitate future UK based lifestyle and therapeutic interventions in addition to effective evidence based T2DM prevention strategies for younger at risk adults. In view of the recent changes within the UK, with the routine care and follow-up of many patients with T2DM increasingly performed in primary care, there is a need to educate primary health care professionals about the additional risks of T2DM in younger adults and ensure that these high risk individuals, who are often difficult to make contact and engage with, have ongoing access to specialist diabetes care as and when required. Furthermore, given the high preponderance of T2DM in young females and the indication for aggressive primary prevention in these individuals which involves potentially teratogenic drugs, it could be argued that all younger woman with T2DM should remain under specialist care to ensure ongoing optimisation of cardiovascular risk and regular pre-conceptual counselling.

Chapter Three: The EXPEDITION study

The EXPEDITION study phenotyped 20 young adults with T2DM, compared with lean and obese control groups and identified that hypertension, dyslipidaemia, a pro-inflammatory state, vitamin D deficiency, low physical fitness and physical activity levels were present in both the obese and T2DM groups, suggesting that obesity rather than T2DM may be driving these changes. However, despite a young age and relatively short duration of diabetes, those with T2DM had evidence of diastolic dysfunction on cardiac magnetic resonance imaging, compared with the obese and lean control groups, suggesting that dysglycaemia rather than obesity may drive this specific abnormality. Although this is a small study, the findings are supported by previous echocardiogram studies from larger studies and the findings raise the possibility that younger adults with T2DM may be at an elevated risk of cardiac failure at an early age (Shah et al. 2011, Whalley et al. 2009, von Bibra et al. 2010). This has implications for clinical practice. There are studies which indicate that weight loss, blood pressure lowering, intensive glucose control and glucagon like peptide-1 (GLP-1) agonist therapy may reverse diastolic dysfunction and could therefore be an indication for more aggressive specialist management of this group (From et al. 2010, Grandi et AL. 2006, von Bibra et al. 2004, Dounis et al 2006, Liu et al. 2010). There is a need for clinical trials to examine the benefits of therapeutic agents and lifestyle interventions in patients with T2DM under the age of 40 years, to identify ways to reduce the future morbidity and mortality from this condition.

Chapter Four: systematic review and meta-analysis

This sedentary behaviour systematic review and meta-analysis identified that excess sedentary time is associated with T2DM, cardiovascular disease, cardiovascular mortality and all-cause mortality, with the most consistent association with T2DM. Importantly, the associations with T2DM and cardiovascular mortality existed independent of physical activity, suggesting that even if an individual meets the physical activity guidelines, their health may still be at compromised if they sit for long periods of time throughout the day.

Despite the inclusion of many large epidemiological studies from across the world, one of the main limitations of these conclusions was reliance of the included studies on self-reported sedentary time, usually television viewing or sitting time. Furthermore, these studies do not account for the possibility of reverse causation. For instance, it is possible that greater sitting or television viewing is a result of poor health rather than its cause. Furthermore, many of the studies failed to account for residual confounding. People who sit more may snack on unhealthy food and drinks and compensate by down regulating healthy aspects of their diet (Andrade et al. 2012). This is supported by the finding that television viewing disrupts the ability to respond to normal hunger and satiety cues, leading to a short term increase in food intake (Wansink et al. 2010, Chapman et al. 2012). In addition, sedentary individuals may work in more stressful desk jobs or have predispositions to other behaviours and experiences which compromise health. These variables are almost

impossible to measure in epidemiological studies and exist as potentially significant confounders. Finally, the data included in the meta-analysis, observational in nature, cannot be used to infer causality.

Nonetheless the findings in this chapter have important implications for modern society, as reflected in the worldwide media attention that the associated Diabetologia publication has caused (Appendix Eight). At present there are no specific recommendations about how much time we should spend sedentary each day and as such, physicians rarely recommend limiting sedentary time to their patients (10% versus 53% for physical activity advice) (Shuval et al. 2012). This is a missed opportunity, particularly for those patients with diabetes who may experience a significant reduction in post prandial glucose by limiting sedentary time (Dunstan et al. 2012, Manohar et al. 2012) or equally those with co-morbidities such as arthritis or back ache who cannot exercise. Reducing sitting time has the potential to prevent T2DM and improve health outcomes but the development of clear and specific public health recommendations will require randomised controlled intervention trials to assess the magnitude of effect of reducing sedentary time.

Chapters Five & Six: STAND methodology

Chapters Five and Six describe the methodology employed in the development and delivery of the STAND programme, a structured education intervention designed to reduce sedentary behaviour in young adults at risk of T2DM. These chapters were informed by widely recognised criteria for

developing and evaluating complex interventions (Medical Research Council, 2008).

Previous sedentary behaviour interventions have been limited to small numbers, often in the workplace setting, with a reliance on environmental prompts for behavioural change. None of the available interventions have targeted multiple sedentary behaviours or employed a structured education approach, combined with self-monitoring, to reduce sedentary time, as in the STAND programme. The approach taken in STAND was novel. However, as one of the first trials to facilitate self-monitoring of sedentary time, one short coming in the development of the intervention was the lack of sedentary behaviour self-monitoring tools designed to meet the specific needs of the trial. As such a suboptimal device, Gruve, had to be selected. In addition to this, there is no validated and reliable posture measurement tool to objectively record sedentary time. As such, the widely used accelerometer, which measures movement intensity but not posture allocation, was used to measure sedentary time, the primary outcome. However, this potentially may have led to inaccuracies in the results obtained in the randomised controlled trial. Both these factors limit the potential impact of the STAND structured education programme. However, this trial identifies some key challenges in future research programmes of sedentary behaviour and will hopefully prompt the wider research community to respond to these weaknesses in measurement and self-monitoring tools.

Chapter Seven: Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from STAND

Baseline data from the STAND cohort provides unique and interesting insights into the prevalence of T2DM in a younger (<40 years) high risk population. T2DM (4.7%) and impaired glucose metabolism (18.1%) were prevalent, comparable to yields obtained for larger population based T2DM screening studies in older adults. Although these data are from a relatively small group, motivated to participate in a randomised controlled trial, which limits the generalisability these findings are timely given the recent introduction of national guidance (NICE 38, 2012) to screen younger adults (<40 years) from high risk ethnic groups and those with predisposing conditions for T2DM. The findings from the STAND baseline cohort lend support to the NICE approach to screening and fill a gap in current knowledge. We now need to ascertain whether traditional approaches to T2DM prevention (structured education, physical activity interventions) which have established efficacy in older adults are equally successful in preventing young at risk individuals from developing T2DM, particularly pertinent in view of the TODAY study which demonstrated that young adult who have already developed T2DM fail to respond to lifestyle and metformin therapy as one would hope (TODAY, 2012).

Chapter Eight: The STAND randomised controlled trial

The STAND randomised controlled trial did not show a significant change in sedentary time at 3 months in the intervention group compared with the control group (-9.74 (-34.27 to 14.79), $p=0.43$). There was a significant

reduction in fasting glucose (-0.52mmol/l (-0.29 to -0.01), $p=0.031$) in the intervention group, in addition to a trend towards improvements in fasting insulin, systolic blood pressure and body fat percentage which just failed to reach statistical significance. No significant changes were found in any other secondary outcomes.

There are a number of methodological issues which may have contributed to the lack of significant difference in sedentary time between the intervention and control groups. The primary outcome measurement tool, the accelerometer, although widely used to measure sedentary time, is a measure of movement intensity and not posture. For instance, standing still may be recorded as sedentary time on the accelerometer due to the lack of movement but this is not sedentary behaviour. Additionally, the accelerometer does not have validated cut points to define sedentary time which further limits the reliability of the findings (Atkin et al. 2012). Further, the lack of valid accelerometer data through the combination of participant loss to follow-up and data loss following processing of the accelerometer files meant that the study was underpowered to see a clinically significant difference in sedentary time. In addition, only 3/4 of intervention participants attended the intervention and of those, only 2/3 used the Gruve self-monitoring tool, many only in the short term. Self-monitoring of behaviour has been identified as a key component to the success of behavioural interventions and the lack of an optimal self-monitoring tool may have also influenced the results obtained (Bandura, 2005). Finally, it remains possible that the group we targeted, obese and young, were not the optimal group for

such a preliminary study. A comprehensive process evaluation will be insightful in unpicking the factors which influenced the failure of the STAND intervention group to significantly reduce their sedentary time. Over and above the issues highlighted, it remains possible that sedentary time is simply so ubiquitous, desirable and necessary in life that reducing sedentary time is not possible for many, despite the will to do so.

The results obtained in this study have implications. There is an international interest in the effects of sedentary behaviour on health, as demonstrated by the international media interest in the publication of the work in Chapter Four (see Appendix Eight). The fact that this trial failed to significantly reduce sedentary time adds to current knowledge and sets other research groups the task of overcoming possible barriers to reducing sedentary time. Future trials will ideally need validated sedentary behaviour measurement and self-monitoring tools which are small and user friendly in addition to environmental and behavioural prompts which are fit for purpose. Short term pilot trials will be required to assess different approaches to reducing sedentary time, in different groups with a detailed analysis of the barriers to behaviour change to inform future large scale intervention trials.

Future directions

Overall, the findings from this thesis have already had a considerable impact. In addition to publications in high ranking journals and presentations at a range of national and international conferences (Appendix Six), some of my work has been highlighted at a symposium dedicated to T2DM in younger

adults at Diabetes UK Annual Professional Conference in 2011. My work has also contributed towards a successful grant application to investigate the effect of GLP-1 analogue therapy on cardiac outcomes in younger adults with T2DM, in addition to assisting in the recent successful application for the University of Leicester to form the NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit.

The results presented in this thesis have some implications for the future. Here I summarise directions for future research for the topics covered within this thesis:

T2DM in younger adults

- Confirmation of the natural history of T2DM in younger adults in long term follow-up studies
- Robust data collection to describe the epidemiology and characteristics of the UK cohort of younger adults with T2DM
- As assessment of the current effectiveness of the current management of T2DM in younger adults (how many are treated with statin and anti-hypertensive agents, have access to specialist care, are provided with regular pre conception counselling etc.)
- The development and evaluation of a structured education programme designed specifically to meet the needs of younger adults with T2DM
- Intervention studies to assess the effects of lifestyle and therapeutic interventions on multiple health outcomes (glycaemic control, weight, complications etc.)

- Further investigation of the efficacy of the NICE recommendations for screening for T2DM in younger adults
- Studies to assess the efficacy of lifestyle/therapeutic interventions to prevent the development of T2DM in younger at risk adults

Sedentary Behaviour

- The development of valid and reliable sedentary behaviour measurement and self-monitoring tools
- Further studies to explore the potential mechanisms linking sedentary behaviour to adverse health outcomes, including the role of lipoprotein lipase in humans
- A detailed assessment of the barriers to reducing sedentary time in addition to the efficacy of behavioural and environmental behaviour change prompts
- Well designed randomised controlled trials to assess whether it is possible to reduce sedentary time and the magnitude of health benefits associated with this, in older as well as young target populations, with a view to developing national and international guidance on sedentary behaviour
- Increase health care professionals awareness of the hazards of excess sedentary time and the potential benefits to reducing sedentary time

Conclusion

We are in the midst of the T2DM epidemic and the programme of research in this thesis has made a unique contribution to bridging gaps in existing knowledge. Specifically, the findings add to our understanding on the impact of a diagnosis of T2DM at a younger age, identifies sedentary behaviour as a risk factor for T2DM, independent of the amount of physical activity undertaken, and provides evidence on the acceptability and effectiveness of a structured education programme designed to reduce sedentary behaviour in young adults at risk of developing T2DM.

Appendix One: Collaborative work: contributions made

Key to contributors

Initials	Name	Role
AA	Arrah Ashu Arrey	Research Nurse
CC	Carolyn Currie	Project Nurse
CE	Charlotte Edwardson	Researcher
CM	Champa Merry	Administrative Assistant
DM	Danielle Morris	Statistician
FA	Felix Achana	Statistician
FP	Frances Pullen	Project Nurse
GPMcC	Gerry McCann	Cardiology senior lecturer
HB	Helen Bray	Project Nurse
HD	Heather Daly	Nurse consultant
HM	Hamid Mani	Doctor
JB	Jane Brela	Health care Assistant
JH	Jayne Hill	Ethics coordinator
JH	Joe Henson	Junior Research Associate
JK	Jamal Khan	Cardiologist
JP	Jennifer Pearson	M.Sc. student, Loughborough University
JR	Jason Rigby	Administrator
JT	Jacqui Troughton	Dietician
JW	Jacqueline Wayte	Project Nurse
KK	Kamlesh Khunti	PhD supervisor
LB	Lesley Bryan	Project Nurse
LG	Laura Gray	Statistician
LM	Lynne Matthews	Project Nurse
MB	Mike Bonar	Education resource development
MC	Marian Carey	National Director:DESMOND
MJD	Melanie Davies	PhD supervisor
ML	Melanie Leggate	Researcher, Loughborough University
MN	Myra Nimmo	STAND and Expedition co-investigator
MS	Martina Sharman	Nurse
NP	Natalie Pearson	Research Assistant for Randomisation
PB	Paul Bray	Administration
RP	Rachel Plummer	Project Nurse
SJHB	Stuart Biddle	PhD supervisor
SM	Samiul Mostafa	Doctor
SP	Shelia Porter	Taskforce Health Care Assistant
SW	Sian Williams	Database manager
TG	Trish Gorely	STAND co investigator
TY	Tom Yates	PhD Supervisor

Overall programme of work

The author of this thesis, Dr Emma Wilmot, performed the following activities in relation to each study contained within this thesis:

Expedition study (Chapter Three)

- obtained ethics and research and development approval
- developed the protocol and study documents
- managed the trial logistics
- performed administrative duties for the study
- managed participant recruitment
- arranged and attended every study visits with every participant
- communicated study results to the patients and their GPs
- analysed and interpreted trial data

Systematic review and meta-analysis (Chapter Four)

- developed the protocol and search terms
- performed the searches, read the abstracts and full text articles
- performed data extraction
- synthesised data into a format suitable for a meta-analysis
- interpretation of the data

STAND programme of work (Chapters Five to Eight)

- obtained ethics and research and development approval
- developed the protocol and study documents
- developed the written structured education curriculum
- managed the pilot and RCT logistics
- data analysis and interpretation

The above activities were performed under the supervision of MJD, KK, TY, and SJHB.

Chapter Three: Expedition study

MJD, MN, GMcC had the original idea for the study. MJD, MN, GMcC, TY, TG, were involved in the development of the protocol. All study investigators (MJD, KK, GMcC, TY, TG, MN) reviewed the study documents which I developed. JH helped review and coordinate the ethics application submission. GMcC performed the cardiac MRI. Cardiac MRI analysis was performed by GMcC and JK. The Loughborough University study visits were overseen by ML. ML performed the VO2 max tests and analysed the inflammatory biomarker data. Towards the end of the study, JR and CM provided administrative support for the study. During the Expedition study I also performed some interviews which have been analysed by TG and JT who were also involved in the development of the topic guides for these interviews.

Chapter Four: Systematic Review

SJHB, MJD, KK and TY helped me to refine the protocol. CE cross checked abstracts, read the full text articles and extracted data in duplicate with me. SJHB, TG, TY, CE and I discussed the findings of the systematic review in detail. LG and FA ran the statistical analysis.

Chapters Five to Eight: STAND programme of work

SJHB, MJD, TY, TG, KK, MN had the original idea for the study. They helped to me to refine the protocol and reviewed the study documents as they were developed. JH helped review and coordinate the ethics application submission. JP was the M.Sc. student who completed the qualitative study for phase 1 of the study. SJHB, TY and CE trialled self-monitoring devices with me for use in the RCT. CE assisted in the development of the written curriculum which was subsequently reviewed by the study investigators (TY, MJD, TG, KK, MN). HD, JT, TG observed and provided feedback on the pilot sessions in phase 2.

A number of administrators worked to ensure the success of the STAND RCT: JR, PB, CM. A number of nurses and health care assistants delivered the study visits: MS, CC, FP, JH, RP, HB, JW, LB, JB, LM, SP. SW led on the GP database searches and managed the study visits performed in Kettering. AA was the nurse who led the Kettering study visits. JH organised some study visits for MRI and DEXA scanning. CE and JH were responsible for accelerometer and ActivPAL data downloads and also led on the processing of the accelerometer data. LG provided statistical input for the trial. Finally, I am extremely grateful to CE who was co-project manager for the STAND RCT. She became the sole project manager for the RCT from June 2011 on when I went onto maternity leave and without her the trial would not have been as successful as it was. On my return from maternity leave I was responsible for data analysis and interpretation.

Appendix Two: Letters and documents related to the conduct of and recruitment to the Expedition study (Chapter Three)

This appendix contains the following, in the order as listed:

- Ethics approval letter
- Participant invitation letter
- Reply slip
- Participant information sheet
- Consent form
- Participant and GP results letters

North Nottinghamshire Research Ethics Committee

4- Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 8526300 (Direct Line)
Facsimile: 0115 9122300

13 March 2009

Professor Melanie J Davies
Dept of Diabetes
Victoria Building
Leicester Royal Infirmary
Leicester
LE1 5WW

Dear Professor Davies

Full title of study:	EXPEDITION: Early detection of cardiovascular dysfunction and health behaviours in the young with type 2 diabetes
REC reference number:	09/H0407/8

The Research Ethics Committee reviewed the above application at the meeting held on 2 March 2009. Thank you for sending Co-Investigators to discuss the study.

Documents reviewed

The documents reviewed at the meeting were:

Document	Version	Date
Participant Consent Form	1	13 February 2009
Participant Information Sheet: Patient Information Sheet	1	13 February 2009
Advertisement	1	13 February 2009
Covering Letter		
Protocol	1	13 February 2009
Investigator CV		
Application	18212/25957/1/579	13 February 2009
GP Letter	1	13 February 2009
Letter of invitation to participant	1	13 February 2009
Interview Schedules/Topic Guides	1	13 February 2009
Statisticalian Comments		13 February 2009
Peer Review		12 June 2008
Summary/Synopsis	Flowchart - Version 1	13 February 2009
Questionnaire: Brief Illness Perception Questionnaire		
Questionnaire: Exercise Self-Efficacy		
Questionnaire: DINE Food Frequency Questionnaire		

Questionnaire EQ-5D		
Questionnaire International Physical Activity Questionnaire (IPAQ)		

Provisional opinion

The Committee would be content to give a favourable ethical opinion of the research, subject to receiving a complete response to the request for further information set out below.

The Committee delegated authority to confirm its final opinion on the application to the Chair.

Further information or clarification required

1. Clarification is required as to what mechanism would be in place should any abnormalities be identified e.g. early cardiac dysfunction etc., will GPs be notified etc.? There should be a clear process to pre-empt this. Provision should be made in the Participant Information Sheet (PIS) and be explicit. A suggested introduction in the PIS could begin 'The tests are not designed for clinical diagnosis, but in the unlikely event that we may find an abnormality....'etc.
2. Clarification is required as to whether you envisage any language problem whilst undertaking the Focus Groups, as it is intended to use non-English speakers, and how any such problem will be addressed
3. A PIS and Consent Form should be submitted to the Committee for the Healthy Volunteer arm of the study
4. On the Consent Form, the statement 'I give consent to be contacted by the School of Sport and Exercise Sciences at Loughborough University with information on further studies that I may be a suitable candidate for', is unclear. Are you seeking consent for Loughborough University to retain a database of personal details on participants? This should be amended to clearly indicate what the participant is agreeing to, and fully explained in the PIS. Also, on the Consent Form, it should be made clearer as to which boxes need to be initialled by the participant in order to take part in the study, and which (if any) are optional
5. In statement no. 1 of the Consent form, the version number and date of the corresponding PIS should be amended accordingly
6. Participant Information Sheet (PIS)
 - There should be a brief explanation of what an MRI scan is. If supplying another document to potential participants e.g. usual hospital information sheet regarding MRI scan, a copy of this should be supplied to the Committee, and also referred to in the PIS
 - Under the heading 'Who has reviewed the study?', the name of the Research Ethics Committee needs amending from 'Leicester' to 'North Nottinghamshire'
 - Under the heading 'What if something goes wrong?' in the PIS, there should be a name and contact telephone number where participants may complain should they wish to. This should be a department independent of the research e.g. the Trust's Patient Advice and Liaison (PALB) service

- Any reimbursement of travel expenses and the maximum amount given, should be detailed in the P18

If you have any queries about the content of this letter, please contact the Co-ordinator.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 11 July 2009.

Ethical review of research sites

The Committee agreed that all sites in this study should be exempt from site-specific assessment (SSA). There is no need to submit the Site-Specific Information Form to any Research Ethics Committee. However, all researchers and local research collaborators who intend to participate in this study at NHS sites should seek approval from the R&D office for the relevant care organisation.

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H0407/8	Please quote this number on all correspondence
------------	--

Yours sincerely

Dr David Walsh
Chair

Email: trish.wheat@nottspcr.nhs.uk

Enclosures:	List of names and professions of members who were present at the meeting and those who submitted written comments.
Copy to:	Mrs Carolyn Burden - R&D Department for NHS care organisation at - UHL



Professor Melanie Davies Professor of Diabetes Medicine, University of Leicester & University Hospitals of Leicester NHS Trust

Dr Ian Lawrence Consultant Diabetologist, Young Adults Clinic, University Hospitals of Leicester

Dr Gerry McCann Consultant Cardiologist, University Hospitals of Leicester

Dr Emma Wilmot Clinical Research fellow, University Hospitals of Leicester

Diabetes Research Department
Level1,
Knighton St OPD
Leicester Royal Infirmary
LE1 5WW
01162047981
Emma.wilmot@uhl-tr.nhs.uk
15/02/10

Invitation to take part in the Expedition Study

(£50 available for participation – see information sheet)

From the information contained within your medical records you have been identified as being suitable for participation in a research study for young people with Type 2 Diabetes. This study is being conducted at University Hospitals Leicester (UHL) and Loughborough University. The title of the study is "The Expedition Study".

EXPEDITION:

Novel Approaches to the Early Detection of Cardiac Dysfunction and Health Behaviours in the Young with Type 2 Diabetes Mellitus

I am enclosing a sheet which provides information about the Expedition Study. If you would like to participate in the study, please complete and sign the enclosed form and return it to Expedition research team in the pre-paid envelope provided.

If you require any further information about the study please contact me via telephone or email as stated above.

Yours sincerely

Dr Emma Wilmot
On behalf of the Expedition Study team



Yes, I would be interested in participating in the Expedition study

☐

Yes, I am interested but would like to discuss the study with you first

☐

No thank you

☐

Please enter your contact details here:

Name _____

Address _____

Phone number _____

Email address _____

Please return this slip with your contact details in the envelope provided.



PATIENT INFORMATION SHEET

Professor Melanie Davies Professor of Diabetes Medicine, University of Leicester and University Hospitals of Leicester NHS Trust

Dr Ian Lawrence Consultant Diabetologist, Young Adults Clinic, University Hospitals of Leicester

Dr Gerry McCann Consultant Cardiologist, University Hospitals of Leicester

Dr Emma Wilmot Clinical Research fellow, university Hospitals of Leicester

Title of project:

EXPEDITION:

Novel Approaches to the Early Detection of Cardiac Dysfunction and Health Behaviours in the Young with Type 2 Diabetes Mellitus

Invitation to participate:

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it involves. This information sheet is designed to help you decide whether you would like to participate in this study. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study and why have I been chosen?

The number of people with type 2 diabetes is increasing dramatically. Type 2 diabetes used to be a condition older people developed. More and more young people are starting to develop this condition. In order to develop appropriate ways of treating diabetes in the young, we need to develop an understanding of why young people develop it and the impact this has on their health. For this study we are looking for people with type 2 diabetes who are less than 40 years of age. We plan to collect data on lifestyle, ability to exercise, diet, heart and nerve function to help us start to develop better education and treatment goals in young people with type 2 diabetes.

Do I have to take part?

It is up to you to decide; participation is voluntary. We will describe the study and go through the information sheet, which we will give to you. We will then ask you to sign a consent form to show that you have agreed to take part, which we will give you a copy of.

V4 270710

You are free to withdraw at any time without giving a reason. The treatment and standard of care you receive will not be affected if you decide not to take part or to withdraw.

What will happen to me if I take part?

Participating in the study will involve two visits and a third optional visit. The following will be recorded:

Visit 1

Visit 1 will be at Loughborough University. At the start of this visit we will record your medical history, blood pressure, height, and weight. We will then ask you to complete some questionnaires which will ask you about your health beliefs, diet and physical activity, followed an interview to explore your thoughts on diabetes. Then, under the supervision of a doctor and exercise specialists you will be asked to exercise to your maximum ability on a stationary bike. We will record your heart rate while you exercise. By doing this we can assess how fit you are and the impact having diabetes has on your ability to exercise. A blood sample will be taken before you exercise and then again afterwards in order to assess the effects of exercise on your body. It is anticipated that visit 2 will take 2-3 hours.

Visit 2

At this visit at Glenfield Hospital 40mls of blood will be taken which will check a range of measures which include diabetes control, vitamin D levels, lipids, thyroid function and measures of inflammation and immune function. A routine ECG (heart trace) will be performed. A cardiac, or heart, MRI scan will be performed. This involves lying still in a tunnel while the machine takes pictures of your heart. Each time we take a picture of the heart we will ask you to hold your breath for around 5-10 seconds. If you are claustrophobic it is unlikely you will be able to complete this test but most people tolerate it very well. During the MRI a drug called adenosine will be administered through a small plastic tube placed in your arm. This drug is short acting but may make your face flush, cause some chest tightness, shortness of breath or dizziness. These effects are short lived (seconds). Through a second vein you will be given an injection of a dye which allows us to measure the blood flow to your heart muscle. More information about this test can be found in the enclosed leaflet "Information for patients having a MRI cardiac stress perfusion scan". After this an echocardiogram will be performed – this takes pictures of the heart and is similar to the scan performed on pregnant ladies to take pictures of their unborn babies.

Physical Activity (visit 1 & 2):

Physical activity will be measured using a meter similar to a pedometer (called an accelerometer and an inclinometer) which is worn on a waist band. It records how much activity you do in a day. This meter will be worn for 1 week, during waking hours, between study visits. To help you to remember to wear the waist band, if you wish, we can send reminder text messages to you.

Visit 3 (optional)

We will do some tests to check your nerve function. This is done by measuring your heart rate response to breathing, lying, sitting, standing and putting your hand in cold water. It is anticipated that visit 3 will last 2-3 hours.

At the end of the study we will write to you with a summary of your personal results. We will reimburse travel costs to a maximum of £50 per visit.

What are the possible benefits of taking part?

You are unlikely to directly benefit from participating in the study. However, by taking part you will be provided with information about how much activity you perform and how your heart functions using the latest technology. The results of this study will be used to improve future assessment and care for patients like you and it is likely you will have a better understanding of why you may have developed diabetes and the effects of this disease on your heart function. If you complete two study visits, we will give you £50 as a thank you for your time and contribution to the study.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the patient advice and liaison service (PALS) are available to provide independent help, advice and support. They can be contacted at:

PALS Office, Glenfield Hospital, Groby Road, Leicester LE3 9QP

Telephone: (0116) 258 3100 E-mail: pals@uhl-tr.nhs.uk

Your legal rights to claim compensation for injury where you can prove negligence are not affected.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Data will be stored either in locked filing cabinets' or in password protected databases which are only accessible by members of the research team. Any information about you which is disseminated will have your name and address removed so that you cannot be recognised from it. Information collected will not be used for any other purpose than that explained here. Your GP will be informed that you are taking part in this study.

What are the risks of taking part?

Taking part involves minimal risk for you, just the inconvenience of taking the time to participate in the study. MRI scanning and exercise tests are very, very safe and both will be monitored by a doctor from the research team. The aim of this study is to develop an understanding of the impact of type 2 diabetes in young people. This will allow us to develop future trials of new treatments and interventions. This study itself will not be of direct benefit to you but it will lead to further research in this area which could improve the treatment of people with type 2 diabetes.

The tests in the study are not designed for clinical diagnosis, but in the unlikely event that we may find an abnormality this will be discussed directly with you. With your permission, we will pass this information to your GP and any relevant specialist(s) with the aim of organising prompt and appropriate investigation and treatment.

Who is organising the research?

This study is being organised and co-ordinated by the University Hospitals Leicester Diabetes Research Group and Loughborough University.

Who has reviewed the study?

This study was reviewed by the *North Nottinghamshire Research Ethics Committee*.

Contact for Further Information

Thank you for taking the time to read this information sheet. The doctors involved in this study will be pleased to discuss any questions or concerns that you may have. If you have any further questions about this research please contact Dr Wilmot on 0116 2047981 or email her at emma.wilmot@uhl-tr.nhs.uk.



Department of Diabetes Research

Chief Investigator: Professor Melanie Davies MBChB MRCP MDFRCP Consultant Physician

Contact: Dr Emma Wilmot, MB ChB B.Sc. (hons) MRCP, Clinical Research Fellow, Tel: 01162047981

Study ID Label

PATIENT CONSENT FORM, Version 4 27/07/10

Title of project: Expedition: Early detection of cardiovascular dysfunction and health behaviours in the young with type 2 diabetes

Chief Investigator Professor Melanie Davies

**Please
Initial Every
Box**

I confirm that I have read and understand the patient information sheet dated 27/07/10 (Version 4) for the above study and have had the opportunity to ask questions.

☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐

I understand that sections of any of my medical notes may be looked at by responsible individuals from the University Hospitals Leicester Research and Development Directorate or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

☐

I agree to take part in the above study, visits 1 and 2.

☐

I also agree to take part in visit 3

☐

Name of patient Date Signature

Name of person taking consent Date Signature
(if different from researcher)

Researcher Date Signature



University Hospitals of Leicester **NHS**

NHS Trust

Leicester Royal Infirmary

University Hospitals of Leicester NHS Trust
Diabetes Research Unit
Leicester Royal Infirmary
Leicester
LE1 5WW
Emma.wilmot@uhl-tr.nhs.uk
Tel: 0116 2047981

«Title» «FirstName» «LastName»
«AddressLine1»
«AddressLine2»
«Town»
«County»
«Postcode»
Date

Dear «Title» «LastName»,

Results from the Expedition Study

Appointment Date
Height: m
Weight: kg
Body Mass Index: kg/m²
Blood pressure: mmHg
Cholesterol: mmol/L
Fasting Glucose: mmol/L

Desirable Values

Body Mass Index: Below 25kg/m²
Below 23kg/m² if South Asian
Blood Pressure: Below 140/85mm/Hg
Cholesterol: Below 5mmol/L
Fasting Glucose: Below 6mmol/L

Heart MRI and echocardiogram:

Accelerometer data:

Average time spent in moderate or vigorous activity/day:

Were the guidelines of at least 30 minutes per day on at least 5 days a week met? Y N

I would like to thank you for attending your appointments with the Expedition Study. Your results and the normal ranges are listed above. Attached is a copy of your activity which was recorded on the accelerometer which you wore. If you would like to discuss your results please do not hesitate to contact me.

Yours sincerely,

Dr Emma Wilmot
Research Registrar, Diabetes & Endocrinology

Results letter for participants Expedition study
V 1 05/10/09



University Hospitals of Leicester NHS Trust
Diabetes Research Unit
Leicester Royal Infirmary
Leicester
LE1 5WW
Emma.wilmot@uhl-tr.nhs.uk
Tel: 0116 2047981

«GP_Title» «GP_FirstName» «GP_LastName»
«PracticeName»
«Practice_AddressLine1»
«Practice_AddressLine2»
«Practice_Town»
«Practice_PostCode»

Date

Dear Dr «GP_LastName»

The following patient has enrolled in the Expedition Study. They attended for fasting bloods, an ECG, echocardiogram and cardiac MRI on «StudyDate». The results are listed below:

Patient: «Title» «Forename» «Surname», «Address1», «Address2», «Address3», «Town», «County», «Postcode».

Date of Birth: «DateofBirth»

Height: «Height» m Weight: «Weight» kg BMI: «BMI» kg/m2

Waist Circumference: «Waist» cm Blood Pressure: «Systolic»/«Diastolic» mmHg

Blood Results:

Total Cholesterol	Result «Total_Cholesterol» mmol/L
LDL Cholesterol	Result «LDL_Cholesterol» mmol/L
HDL Cholesterol	Result «HDL_Cholesterol» mmol/L
Triglycerides	Result «Triglycerides» mmol/L
Sodium	Result «Sodium» mmol/L
Potassium	Result «Potassium» mmol/L
Urea	Result «Urea» mmol/L
Creatinine	Result «Creatinine» umol/L
eGFR	Result «eGFR» mL/min
HbA1c	Result «HbA1c» %
Fasting Glucose	Result «Fasting_Glucose» mmol/L

Cardiac MRI:

Yours sincerely

Dr Emma Wilmot
Research Registrar, Diabetes & Endocrinology

GP results letter for participants in the Expedition study
V1 05/10/09

Appendix Three: Supplementary material for the systematic review and meta-analysis (Chapter Four)

Search terms used

Sedentary behaviour search terms:

exp SEDENTARY LIFESTYLE/
"sedentary".ti,ab
"non exercise".ti,ab
"non leisure".ti,ab
"inactivity".ti,ab
"physic* inactiv*".ti,ab
"television watch*".ti,ab
"TV watch*".ti,ab
"television view*".ti,ab
"TV view*".ti,ab
"screen based".ti,ab
"computer use".ti,ab
"computer gam*".ti,ab
((screen adj2 time)).ti,ab
"couch potato".ti,ab
"sitting".ti,ab
"car use".ti,ab
((car adj4 driv*)).ti,ab
((car adj4 rid*)).ti,ab
"low physical activ*".ti,ab
"IPAQ".ti,ab
"international physical activity questionnaire".ti,ab

Diabetes search terms:

exp DIABETES MELLITUS, TYPE 2/
"Type 2 diabetes".ti,ab
"Type II diabetes".ti,ab
"non insulin dependent diabetes".ti,ab
"niddm".ti,ab
"T2DM".ti,ab

Glucose and insulin terms:

exp INSULIN
"insulin".ti,ab
Exp GLUCOSE
"glucose".ti,ab
"HOMA".ti,ab

Metabolic syndrome search terms:

exp METABOLIC SYNDROME X/
((metabolic adj3 factors)).ti,ab
((clustering adj3 risk factors)).ti,ab
"cardio-metabolic".ti,ab
"cardiometabolic".ti,ab

Cardiovascular disease search terms:

exp CARDIOVASCULAR DISEASES/
exp CORONARY DISEASE/
"coronary heart disease".ti,ab
"coronary artery disease".ti,ab
"myocardial infarct*".ti,ab
"cardiovascular".ti,ab
exp STROKE/
"stroke"
(cerebral adj2 accident)
(cerebral adj2 infarct*)

Mortality search terms:

exp MORTALITY/
"death".ti,ab
"survival".ti,ab

Study type

exp CROSS SECTIONAL STUDIES/
cross sectional
exp PROSPECTIVE STUDIES/
prospective
exp FOLLOW-UP STUDIES/
Follow-up
exp COHORT STUDIES
cohort
hazard ratio
relative risk
observational stud*

Limits

[Limit to: Humans and English Language]

Appendix Four Supplementary material related to STAND phases 1 and 2 (Chapter Five)

This appendix contains the following, in the order as listed:

- Pilot workshop feedback form
- Pilot session feedback
- Example of the STAND curriculum
- Participant resources
 - Preparing for STAND
 - My risk factors
 - My health profile
 - What am I going to do now

Your thoughts on the workshop.....

Best bits



.....



.....



.....

What do you think was the key message(s) of the workshop?

IDEAS for improving



.....



.....



.....

What I didn't enjoy



.....



.....



.....

Thank you for your time.

Workshop evaluation V1 011209

Your thoughts on doing less sitting

When do you think it will be easiest to do less sitting?



.....



.....



.....

IDEAS for helping others in the future to sit less



.....



.....



.....

When do you think it will be more difficult to sit less?



.....



.....



.....

Other comments on being asked to sit less

Thank you for your time.

Workshop evaluation V1 011209

The level of the workshop was...	too easy <input type="checkbox"/>	about right <input type="checkbox"/>	too difficult <input type="checkbox"/>
The length of the workshop...	too short <input type="checkbox"/>	about right <input type="checkbox"/>	too long <input type="checkbox"/>
What do think about the venue?			
What is the best time to hold a workshop?			

Other comments and any other topics you'd like to know more about

Thank you for your time.

Workshop evaluation V1 011209

Pilot session feedback

(STAND team responses in italics)

STAND Pilot 1, feedback facilitated by JT:

Best bits of the pilot:

- Discussing the plan to reduce sitting time
- Guessing the time spent sitting time
- Activity summary from ActivPAL
- Explanation of diabetes
- Different risk factors for diabetes
- Creating ideas how to reduce sitting time
- Dismissing the myths about sugar

Ideas for improvement:

- Educators to provide “ideas for pc work while standing up & how to convince people in a meeting to stand up”
These ideas should ideally come from the group to promote systematic rather than heuristic processing
- Add step count to activity discussions
We subsequently advised participants to ignore step count in the ActivPAL feedback as this was not the main focus of the intervention
- Describe how to do a diabetes test
Not relevant as participants in the randomised controlled trial will have had a OGTT and Hba1c by the time they attend the course and would know this in advance
- Make a nice poster of the man
A drawing allows for more interaction than a poster
- More time for planning/goal setting
This is a crucial part of the education session so we ensured enough time was allocated to make sure this section was not rushed
- Could have been more positive than negative (risk of heart attack, cholesterol, blood pressure etc)
More emphasis was put on the benefits of reducing sitting in the curriculum
- Setting the long term goal is difficult. Could it be more specific eg 1 hour reduction in sitting time, then it would be easier to set short term goal
We will be more directive if required and will make it explicit that the trial recommends a minimum reduction of 1 hour per day sitting time, but ideally the participants should aim to set their own realistic goals
- Risk analogy contrived – try crossing road/driving.
Team discussed this and felt driving/crossing the road would lose impact when communicating what risk means

Other feedback:

- Length of workshop about right
- Evening courses preferable
We will offer these in the RCT
- Level of workshop just right (1 said too easy but this was delivered to a group of post grads)

- Key message were correctly identified
- Resources were self explanatory, some did not like the dead man or tired man
Alter images
- JT felt the images were stereotypical with men in male roles etc.
More female images added, fat man should be fatter.

STAND Pilot 2 feedback, facilitated by TG

Best bits of the pilot:

- Helpful facilitators
- Workshop was well planned
- Very active in terms of visual content
- Finding out more info about diabetes and insight into how to prevent it
- Looking at activity feedback results

Ideas for improvement:

- More breaks
This particular group opted to stay in their seats during the break – so even during the break they did not get up to move around/eat. Not sure further breaks would have helped?
- activPAL to work
There was some teething problems with the ActivPAL function which was resolved prior to the randomised controlled trial.
- Why picking standing? Commonsense says eating healthily or more vigorous exercise might have more impact
The educators increased the emphasis on the current evidence to support these strategies and to stress that reducing sitting is an additional benefit
- 1 person did not like the metaphor
Recurring theme – also from the Walking Away study. Discussing with WA investigators, they feel alternative metaphors will have less impact

Other feedback:

- Length of course was good
- Best time for workshop is afternoon/evening
We will offer these times in the RCT
- Level of workshop was about right (1 said too easy, again 50% of this group were post grads)
- Venue adequate
- One person would like to know more about diabetes
We planned to stress the opportunity for further questions at the end or during the break
- One person wanted to know how much behaviour change is needed for diabetes prevention
There is currently no evidence based answer to this question with regards to reducing sitting time

During discussions the participants suggested that providing the summary feedback from the activePAL as averages across the assessment days would be helpful – eg average time spent sitting. The hour by hour graphs can stay as they help identify time specific blocks of sitting, but the top level

of “on average you sit for X hours a day” was thought to be a more powerful message as a starting point.

Written STAND curriculum: example session

Session F: Sedentary Behaviour

Duration: 105 minutes

Participant learning opportunities:

Participants will:

- Know the complications associated with sitting for long periods
- Know the benefits of reducing sitting time
- Know how long they spend sitting each day and identify what sitting activities they do
- Set a plan of action to reduce their sitting time
- Know how to use the self-monitoring tool

Content covered:

- The main complications associated with sitting for long periods
- Estimates of sitting time and objective level of sitting time
- Identifying main sitting time during the day and main sitting activities engaged in
- Weighing up pros and cons of sitting less
- Short term and long term goals
- Barriers to sitting less
- Using the self-monitoring tool to reduce sitting time

Educator activity:

- Ensures that all participants are able to contribute in a way in which they feel comfortable, by acknowledging all contributions and thanking them for their contributions
- Uses open questions to check understanding
- Refers participants to comment on the flip charts at appropriate points

Participant activity:

- Works out the common complications associated with sitting for long periods
- Works out the benefits of reducing sitting time
- Estimates their own sitting time
- Views objectively measured sitting time and reflects on this
- Identifies sitting activities and ways to reduce sitting time
- Sets goals for sitting less
- Identifies barriers that might be experienced when trying to sit less
- Learns how to use the self-monitoring tool

Resources required:

- Magnetic board
- Magnetic representation of complications
- Flip chart and pens
- 'What I am going to do?' booklet
- ActivPAL feedback sheets
- Gruve devices
- Gruve instructions

Session F: Sedentary Behaviour

We're going to move on now to look at sedentary behaviour in this section

Health Consequences of Sitting for Long Periods

Sitting down is something most of us have to do, whether we work at a computer or not, most jobs require at least part of the day to be spent sitting. Unfortunately sitting for too long can cause a range of health issues, even for those people who take part in physical activity regularly. For example, if someone got up and went to the gym for 30 mins and then went to work and sat at a desk all day and then went home and sat in the evening, even though they did their physical activity that day evidence has shown that their health may still be at risk because of the large amount of sitting time.

Does anyone know about any of the health consequences of sitting for long periods of time? (Use magnetic pieces and prompt participants for answers)

- **Obesity** (One study compared workers who spent the majority of their day sitting to workers who spent the majority of their working day standing and found that the workers whose job involved standing burned 800 more calories than the workers whose job involved sitting. 800 calories would be equivalent to running 5 miles. So standing more throughout the day can help with weight management).
- **Diabetes**
- **Heart disease**
- Numerous studies are starting to show that the rates of heart disease, diabetes and obesity are doubled or sometimes even tripled in people who sit a lot.
- **Cancer**
- **Deep vein thrombosis** (people who sit at their desks for prolonged periods of time face a high risk of developing blood clots in the legs)
- **Back and neck pain**
- **Premature death**
- **Fatigue** (People who lead sedentary lifestyles reported feeling more fatigued)
- **Sleep problems** (People who lead sedentary lifestyles may find it difficult to sleep at night because of their inactivity during the day. This

includes not only getting to sleep but how many times you wake up in the night)

So if these are the consequences of sitting too much, what do you think the benefits of reducing sitting time might be? Sitting less can help with reducing your risk of developing type 2 diabetes, your risk of developing heart disease as well as help with many other conditions. (Use magnetic pieces)

To put sitting in the context of diabetes, what is the first thing that starts to go wrong in the body of people with Type 2 diabetes?

Yes that's right, the locks are rusty (insulin resistance)

How does sitting for long periods affect the rusty locks?

Collect answers, acknowledge responses and try to elicit the following:

Sitting for long periods of time makes the locks on the muscle cells more rusty and stops glucose from entering the muscle cells. Standing activates the largest muscles in the body, when standing these large muscles are being used which has a positive impact on the rusty locks so standing up and moving around regularly can help reduce 'insulin resistance'.

Reflection on sitting time and personal feedback

We are now going to move on and think about the time we spend sitting each day (before work, at work/during the day, in your leisure-time). Think about a typical day, What sitting activities are you doing? Give an example from your day e.g., sit to eat my breakfast, sit on the train to work, sit at my desk, sit to eat lunch, sit to watch TV, sleep.

Give people time to reflect and jot down there sitting activities. Remind them to include sleep.

Thinking about these activities, how much time do you think you spend doing each of these activities? Adding all of the activities up, how much time do you think you spend sitting each day e.g., 10 hours, 15 hours etc?

Encourage people to write these estimates on a piece of paper and reflect on the time spent sitting.

Now we are going to compare your estimate with the sitting time from the monitor you wore on your thigh for 10 days. This monitor measured by amount of time you spent sitting, standing and walking.

Talk through an example feedback sheet and then hand out feedback sheets to participants. Only look through summary sheet for each day first. Give participants a chance to reflect on their results individually.

What so you think about your current sitting time? How does this compare to your earlier estimate? Are you doing more or less sitting than you thought?

Listen to answers

Ask participants to mark their average sitting time in my health profile and in the 'What am I going to do now?' booklet.

The other sheet in your feedback gives you a breakdown hour by hour for each day. Each row represents an hour and the yellow indicates sitting, green indicates standing and red indicates stepping. Go through an example.

From your feedback can you identify which part of the day you spend most of your time sitting? What activities are you doing?

Let participants identify the activities that they are doing during this time and encourage them to write these down on their feedback sheets.

So which part of the day are you spending most of your time sitting?

Get answers from the group and note different parts of the day on flip chart paper as headings

What sitting activities are you doing during these parts of the day?

Go through each part of the day participants have identified i.e., in the evening, at work etc

So now we have a list of sitting activities that you all do lets see if we can come up with some ideas of how we can reduce sitting time.

Write solutions on the flipchart next to the activities identified. Generate a discussion within the group on ways to reduce sitting time.

Possible ways to reduce sitting time

At the start of the day:

Some of the possible ideas could include:

- Standing whilst eating breakfast
- Standing whilst drying hair/applying make up
- Having a shower instead of a bath
- Standing whilst reading the newspaper

At work:

Some of the possible ideas could include:

- Active emailing
- Standing whilst on the telephone
- Standing during a coffee break
- Walk to a toilet, water fountain, or photocopier on a different floor
- Swap your chair for one without wheels or take the wheels off
- Standing for part or all of a meeting
- Standing during lunch breaks
- Move your bin across the office
- Standing at regular intervals

Commuting:

Some of the possible ideas could include:

- Park your car further away from your destination
- Use public transport
- Stand whilst waiting for a bus or train
- Stand for part or all of your bus or train journey

Time at home:

Some of the possible ideas could include:

- Standing during adverts
- Put the remote on top of the television
- Stand during telephone calls
- Stand whilst making dinner
- Stand whilst surfing the internet
- Standing playing computer games e.g., Wii games

Socialising:

Some possible ideas could include:

- Standing in the pub
- Visit friends instead of phoning
- Go shopping with friends

Looking at the solutions we have come up with to reduce sitting time, which ones do you think you could incorporate into your daily lives?

Encourage participants to get out thier booklet 'What am I going to do now'? and ask them to fill in the things they could do to sit less.

Goal Setting

Weighing up change: the pros and cons of sitting less

Now that we have some possible solutions that you could incorporate into your life, you need to decide whether it is actually going to benefit you to reduce your sitting time. So in your booklet there is a space for you to note down the benefits of reducing sitting time and the disadvantages of reducing sitting time.

What would be the benefits of reducing your sitting time? (refer back to magnetic pieces on health consequences)

Encourage participants to fill in their "pros" section in the 'What am I going to do now?' booklet.

What would be the disadvantages to reducing your sitting time?

Encourage participants to fill in their "cons" section in the 'What am I going to do now?' booklet.

Overall looking at your pros and cons do you think that it is worth reducing your sitting time?

If you have decided that you really would benefit from changing your sitting behaviour the next stage is making a plan.

Why do you think that making a plan can help you to reduce your sitting time?

Elicit answers: They are more likely to get started.

Long Term Goal - 60 minute recommendation

When making a plan the first thing we need to think about is a long term goal i.e. how much do you want to reduce your sitting time by in the long term.

Does anyone know how much you need to reduce your sitting time by to see health benefits?

Once suggestions have finished, clarify.

This study recommends that you reduce your sitting time by at least 60 minutes a day. The researchers who designed this study estimated that 60 minutes a day may be enough to improve blood pressure, cholesterol and risk of diabetes. If you could look at the top of the page in your booklet you have a space for a long term goal. Your long term goal needs to be realistic for you but it would be good if it could be at least 60 minutes and don't forget to put a time limit on when to achieve it by e.g., 6 months, 1 year etc.

Ok, so you've set your long term goal, if your long term goal is a 60 minute reduction in sitting time, do you think you have to aim for the 60 minute reduction all at once?

Collect answers and acknowledge responses. Elicit: No it does not have to be done all at once, you could start off by making small changes. For example:

I could start off by standing during my coffee break and standing to talk on the telephone. When I felt confident I could do that, I could also stand during television adverts and leave the remote on the television. So I could set myself short term targets to achieve.

What do you think is a sensible amount to reduce sitting time by initially?

Reducing by 10 or 15 minutes would be a realistic achievable amount initially. This would be your short term goal. It is better to build up to your long term goal slowly to make lifestyle changes sustainable.

Why is it important to set short term goals?

Collect answers and acknowledge responses

Setting short term realistic goals makes it easier to reach your target and makes you less likely to fail.

Now you can set yourself a short term goal and don't forget to put a time limit for it e.g., 1 week, 1 month etc.

What am I going to do to reach my short term goal?

Encourage participants to look back at the activities they identified earlier in the booklet.

When am I going to do it?

Encourage participants to identify when during the day they will target the behaviour that they will change e.g., at work, in the evening etc.

Barriers to reducing sitting time

There will always be things that get in the way of you reducing your sitting time and achieving your goals. These things are called barriers. An example of a barrier to reducing my sitting would be my job because I am expected to sit at my desk a lot.

Let's think about barriers as a group. **What might make it difficult for you to reduce your sitting time?**

Encourage participants to relate barriers to the activities they have chosen to do to reduce their sitting time. Ask people to identify the barriers and write on flip chart paper. Acknowledge responses:

Okay thank you for sharing those barriers. **Can anyone think of solutions to these problems?**

Facilitate some discussion around managing barriers.

Why do you think it can be useful to think about barriers to reducing sitting time?

Because then you can put in place plans to stop failing.

What is going to stop me?

Encourage participants to complete the barriers section in the booklet.

How am I going to overcome my barriers?

Identify what they can do to overcome their barriers so that they will achieve their goals. Write in booklet.

What support might you need to enlist to help you with your plan?

Elicit answers and ask people to complete the section 'What support might I need?'. Go around the room to help people.

Once they have done this then ask them:

I would like you to think about your plan and decide how confident you are that you will do it. To do this use the 1-10 scale, where 1 is 'there is no way I will be doing this in 3 months time' and 10 that you are 100% certain that you will be doing this in three months time. Write this in the confidence box in your action plan.

Pause for a moment to give everyone a chance to do this and think about your action plan and give it a number. Then in your own words:

If you find you have given yourself less than a 7, we would like you to think about your action plan and decide how it needs to be changed to be at least a 7. Then write down this new plan.

Pause for a moment to give everyone a chance to re-evaluate their confidence.

What could you do to increase your confidence to achieve your plan?

Elicit answers and ask people to complete the section 'What can I do to increase my confidence?'

Go around the room to help people.

When will you start your action plan?

When can it be useful to review your plan?

Elicit answers and ask people to complete the section 'When will I review my plan?' Go around the room to help people.

When you review your goal and you have achieved it what would you do?

Elicit: Yes that's correct you would set yourself another short term goal because don't forget you are working towards that long term goal.

What happens if you review your plan and you haven't achieved your goal?

Elicit: Yes that's correct you would look back at your plan and think about why and then reset your goal.

Reviewing and setting short term goals is something that you need to do continually until you have reached your long term goal.

When you have been making a lifestyle change for a while what sometimes happens?

Elicit: harder than planned etc.

How often do you think people relapse when they make a change?

In previous studies where people tried to stop smoking, it was 3-7 times with the average being 4 times.

What are the benefits of a relapse?

Learn from experience and re evaluate the plan.

Self-monitoring

Now we have come up with a plan of how we will reduce our sitting time I would like to give you a device to use over the course of the study that will record your sitting time and also vibrate when you have been sitting for a long period of time. **So how can recording your sitting time help you?**

Elicit answers:

Lets me see how I am doing

It helps me keep on track

It allows me to see good and bad days

Helps me see barriers and plan solutions

This is the monitoring device and it's called the Gruve. I'm just going to demonstrate how to use it and how to wear it correctly.

Hand out a Gruve to each person and go through the instruction sheet.

Any questions about the Gruve?

Preparing for **STAND**

This booklet aims to answer some basic questions about your risk and gives you a better idea of what coming to a **STAND** workshop is all about



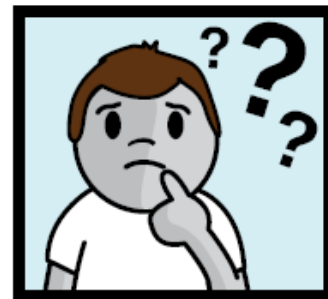
So you have been told that you may be at risk of developing Type 2 diabetes...

There are many questions you will want to have answered. Coming to a STAND workshop is the start of answering these questions.

STAND helps you to begin to manage your risk. This leaflet can't answer all of your questions, but it will help you to have a better idea of what will happen on a STAND course

So, what does it mean to be at increased risk of developing Type 2 diabetes?

- You are more likely to develop Type 2 diabetes in the future.
- You have an increased chance of having high blood pressure, high cholesterol, heart disease and stroke in the future.



And now for the good news!

We know that you, and others like you at risk, can do quite a lot to reduce your risk of developing Type 2 diabetes and other problems.

The best way you can manage your risk is by making changes to your lifestyle by:

- Decreasing the amount of sitting that you do
- Maintaining regular physical activity
- Maintaining a healthy diet
- Working together with professionals
- Making use of the regular check-ups that you will be offered in the STAND study

What changes should I start making now?

Even simple changes can make a difference, such as being more active. Did you know that just standing up, instead of sitting, can help reduce your risk of diabetes?

Before the workshop, begin to think about ways to reduce the time you spend sitting, for instance:

- Standing whilst on the telephone
- Move your waste bin across the office
- Standing during TV adverts

Obviously these are very individual choices, and you will have time to think about them at your STAND course.



What about my feelings?

By now, you may have had the chance to speak to your family doctor or nurse. You may also have had a phone call from one of the STAND team. You may want to talk to your friends and share your thoughts and feelings about finding out your risk.

- Are you surprised?
- Are you frustrated or angry?
- Are you worried?

Feeling surprised is quite common, as people at risk may not feel unwell. It is hard to believe what the doctors or nurses say. Some people find it quite a struggle to think about changing their lifestyle when they actually don't feel unwell. This is why it's important to understand what is happening to your body with this risk, and why attending a STAND course will help this understanding.

Feeling frustrated or angry? You might think it is unfair. It might have come at a bad time, when you have other important things going on in your life.

Feeling worried because you may have heard bad stories about diabetes? Being at risk you are in no immediate danger, and can reduce your chances of having health problems by being involved in looking after your own risk.

What is STAND all about?

STAND helps you to get started by looking after your risk.

At STAND you can:

- Talk about your concerns
- Get answers to your questions
- Discuss the options for reducing your risk
- Be supported in making your own choices about how you deal with your risk
- Find out about what support you can expect from your local health service

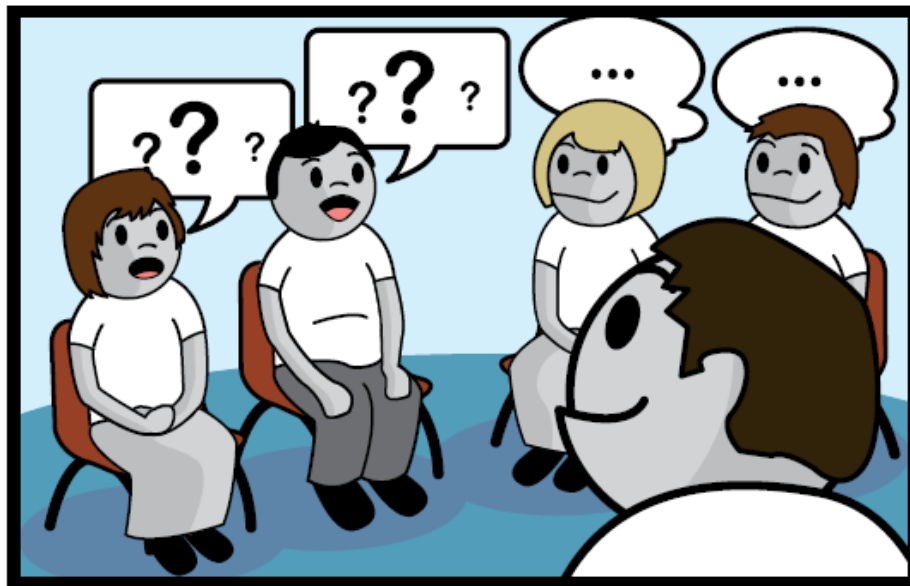
STAND is run in groups because:

- It's good to talk to people in a similar situation
- People can learn from each other
- People can often help each other and share ideas
- People enjoy the sessions - even if they come along thinking they won't!

The sessions are relaxing, friendly and fun. Because the numbers in the group are small, it's more like being among friends. The sessions are run by specially trained professionals.

This training means they are able to:

- Answer your questions
- Support and encourage you



What can I do to get ready for STAND?

You may feel that you have enough to think about right now, and would just like to come along on the day, and take it from there. But if you want to prepare for your STAND session, you may want to think about the following:

What do you want to know?

What are the questions that you or your family have at the moment about your risk? Are you unsure as to how it will affect your life? Jot down some questions - it's easy to forget them on the day:

Notes -

Sitting Time

You may not be aware but sitting for long periods plays a large part in increasing your risk of developing health problems. It might help you to think a little about much time you spend sitting before you start STAND. Sitting less does not mean that you need to join a gym, it is about you trying to break up and reduce your sitting time and move around as much as you can and as often as you can.

Answer the questions below by ticking either Yes or No and then estimate how long you spend sitting.

	Yes	No	Roughly how long each day?
Do you spend time sitting at a computer?			
Do you spend time sitting watching TV?			
Do you spend time sitting whilst commuting?			
Do you spend time sitting at work?			

How did you do?

The more hours you spend sitting each day the more you are putting your health at risk. These are things you can discuss at STAND.



And finally...

You now probably have the information you need. If you have any urgent questions which you need answering before you come to STAND, please contact your doctor or nurse.












We look forward to welcoming you to STAND

My Risk Factors

This worksheet will help you to assess the health risks currently in your life



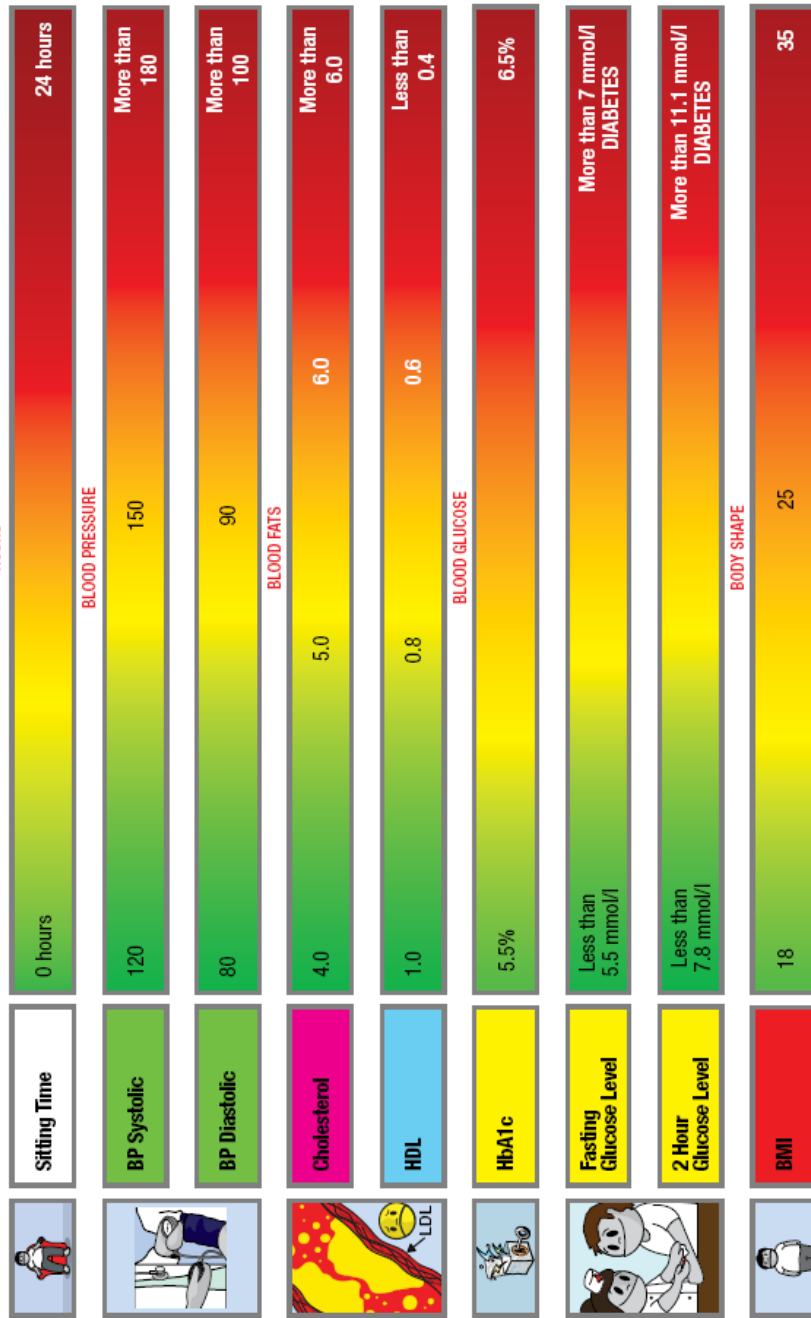
My Risk Factors

Risk Factor		My Risk Factor	Can I change this risk factor?
South Asian or African Caribbean			
Family History of Diabetes			
Getting Older			
Abnormal Blood Glucose			
High Blood Pressure			
High Blood Cholesterol			
Sitting For Long Periods			
Weight Around the Middle			
Eating Saturated Fat			
Depression or Chronic Stress			
Poly cystic ovarian syndrome			

My Health Profile



My Health Profile



What Am I Going To Do Now?

This worksheet will help you to plan changes you can make to your lifestyle.



Current Sitting Time: hours

Reducing sitting time: Possible solutions include:

Activities to break up sitting time:

- | | |
|----|----|
| 1. | 2. |
| 3. | 4. |
| 5. | 6. |
| 7. | 8. |

Pros and cons of sitting less:

Pros

- | | |
|----|----|
| 1. | 2. |
| 3. | 4. |

Cons:

- | | |
|----|----|
| 1. | 2. |
| 3. | 4. |

Long Term Goal: Reduce sitting by: minutes/days by Date

Short Term Goal: To reduce my sitting time by <input type="text"/> minutes by <input type="text"/> Date	
What am I going to do?	
1.	2.
3.	4.
When am I going to do it?	
1.	2.
3.	4.
What's going to stop me?	
1.	2.
3.	4.
How am I going to do this?	
1.	2.
3.	4.

What support might I need?

- | | |
|----|----|
| 1. | 2. |
| 3. | 4. |

How confident am I?

How confident do I feel that I can sit less? (Choose a number between 1 and 10 where 1 is not at all confident and 10 is very confident)

The number I choose is:

What can I do to increase my confidence?

- | | |
|----|----|
| 1. | 2. |
| 3. | 4. |

When am I going to start?

Date:

When will I review my plan?

Date:

Appendix Five Supplementary material related to the STAND randomised controlled trial

This appendix contains the following, in the order as listed:

- Ethics approval letter
- Clinical trial registration information
- Documents for recruiting GP practices
- Participant letter of invitation
- Reply slip
- Patient information sheet
- Consent form
- Results letters for participants and GPs
- Booklet send to the control arm participants
- Examples of questionnaires in Chapter Eight
 - Short IPAQ
 - Marshall sitting survey

National Research Ethics Service

Nottingham Research Ethics Committee 1

1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 01158839425
Facsimile: 01159123300

07 May 2010

Professor Stuart Biddle
Professor of Exercise and Sport Psychology
Loughborough University
School of Sport, Ex & Health Science
Loughborough University
LE11 3TU

Dear Professor Biddle

Study Title: An intervention to decrease sedentary behaviour in young adults at risk of type 2 diabetes: project STAND (sedentary time and diabetes)
REC reference number: 10/H0403/13
Protocol number: 1

Thank you for the email of 29 April 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the
National Patient Safety Agency and Research Ethics Committees in England

10/H0403/13 Further information favourable opinion letter reissued to correct document names. 23/07/2010

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

Other conditions specified by the REC:

- The study protocol should include a statement that the heparin injection is optional.

The final version of the Protocol should be provided to the committee for information only.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		
REC application	43915/89914 /1/435	12 January 2010
Investigator CV	2	16 November 2009
CV - Melanie Jane Davies	2	27 March 2009
CV - Emma Wilmot	2	21 December 2009
Participant Information Sheet: PHASE 1	1	01 December 2009
Participant Information Sheet: PHASE 2	1	01 December 2009
Letter of invitation to participant	PHASE 1 - 1	01 December 2009
Letter of invitation to participant	PHASE 2 - 1	01 December 2009
Letter of invitation to participant	PHASE 3 - 1	01 December 2009
Participant Consent Form: PHASE 1	1	01 December 2009
Participant Consent Form: PHASE 2	1	01 December 2009
STAND Advertisement	1	01 December 2009
Workshop Evaluation	1	01 December 2009
Instruction Sheet - Accelerometer information	1	01 December 2009
STAND Phase 3 Control Arm Booklet	1	01 December 2009
STAND appointment letter	1	01 December 2009
Referees or other scientific critique report		15 May 2009
Accelerometer - Reminder	1	01 December 2009
Project STAND recruitment email	1	01 December 2009
Phase 3 GP invitation letter	1	01 December 2009
Topic guide DM risk	1	01 December 2009
Educator Training	1	01 December 2009
Phase 3 Process Evaluation Topic Guide	1	01 December 2009

10/H0403/13 Further information favourable opinion letter reissued to correct document names. 23/07/2010

Technology topic guide	1	01 December 2009
Project STAND Overview	1	01 December 2009
Project STAND Milestones	1	01 December 2009
STAND: Participant flow chart	1	01 December 2009
GP results letter for participants in project STAND	1	01 December 2009
STAND participant result - normal	1	01 December 2009
STAND participant result - pre diabetes	1	01 December 2009
STAND leaflet	1	01 December 2009
Sitting Survey	1	01 December 2009
Pedersen's Polycystic Ovarian Syndrome Screening Tool		
Marshall Sitting Survey: Total and Domain Specific sitting time		
Brief IPAQ		
International Physical Activity Questionnaire		
Hospital Anxiety & Depression score		
Exercise self-regulatory efficacy questionnaire		
Exercise self-efficacy		
EQ-5D		
Brief Illness Perception Questionnaire		
Protocol	2	10 March 2010
Participant Consent Form: PHASE 3	2	10 March 2010
Response to Request for Further Information		10 March 2010
Participant Information Sheet: Phase 3	3	29 April 2010
Response to Request for Further Information	Email	29 April 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our

10/H0403/13 Further information favourable opinion letter reissued to correct document names. 23/07/2010

service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0403/13

Please quote this number on all correspondence

Yours sincerely

PP 

Mr Robert Johnson
Vice Chair

Email: trish.wheat@nottspct.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: R&D Department for NHS care organisation at lead site – UHL
Student – Dr Emma Wilmot

Clinical trial registration

Clinical Trials.gov identifier: NCT01301196

Available at:

[http://www.clinicaltrials.gov/ct2/show/NCT01301196?term=sedentary&type=I](http://www.clinicaltrials.gov/ct2/show/NCT01301196?term=sedentary&type=I&rank=2)
[ntr&cntry1=EU%3AGB&rank=2](http://www.clinicaltrials.gov/ct2/show/NCT01301196?term=sedentary&type=I&rank=2)

MRC91409



University Hospitals of Leicester NHS Trust
Diabetes Research Unit
Leicester Royal Infirmary
Leicester
LE1 5WW
Emma.wilmot@uhl-tr.nhs.uk
Tel: 0116 2047981
XX/XX/XXXX

GP Address

Dear Dr

STAND: Sedentary Behaviour and Diabetes

I am writing to invite you to participate in what will be an important development for people with a high risk of developing type 2 diabetes and their health care providers within Leicestershire. This study, funded by the Medical Research Council, is being led by Professor Stuart Biddle (Loughborough University), Professor Melanie Davies (Leicestershire Diabetes Research Team) and Professor Kamlesh Khunti (Professor of Primary Care). It is an innovative proof of concept study aimed at reducing sedentary behaviour in young people who have a high risk of developing diabetes.

The study aims to recruit 178 overweight and obese adults between the ages of 18 and 40 years. Inclusion criteria are:

Age 18-40 years plus a BMI $\geq 30\text{kg/m}^2$ ($\geq 27.5\text{kg/m}^2$ for south Asians) OR

Age 18-40 years with a BMI $\geq 25\text{kg/m}^2$ ($\geq 23\text{kg/m}^2$ for south Asians) plus one of:

- family history of diabetes or cardiovascular disease in a first degree relative;
- previous gestational diabetes or PCOS;
- HbA1c $\geq 5.8\%$ and/or impaired glucose regulation

Individuals meeting the inclusion criteria will be invited to participate in the STAND randomized controlled trial where they will be assigned to either a structured education programme aimed at reducing the risk of type 2 diabetes through decreasing sedentary behaviour or standard care. All individuals recruited into the study will receive a full oral glucose tolerance test at baseline, 3 and 12 months. In addition, we will also measure a full lipid profile and blood pressure at each of these time points along with other important and lifestyle variables. You will be informed of the results for each patient. If you agree to take part in this study we will offer you a one off payment and administration costs will be provided.

If you would like to take part or require further information please complete the enclosed document and return it to us in the prepaid envelope provided. Alternatively, contact XXXX the study manager at XXX@XXX. We will then arrange for a member of our research team to attend your practice and discuss the study further.

We look forward to hearing from you.

Yours Sincerely,

Professor Stuart JH Biddle
Loughborough University
Chief Investigator.

Professor Melanie Davies
University of Leicester
Principal Investigator

Professor Kamlesh Khunti
University of Leicester
Principal Investigator

Phase 3 GP invitation letter V2 161110

Name / Address of Practice

We would like to hear more about the STAND study ☐

*We **do not** wish to hear more about the STAND study* ☐

Name of Staff Member to Contact

Best time to contact:

Email address:

Phone number:

Yours sincerely



GP headed notepaper

Name
Address
Address
Address

Date

Dear

Invitation to join a diabetes prevention study – “STAND”

In the UK the number of people with diabetes is increasing. Some young people are more at risk than others, depending on whether they have certain risk factors present such as age, body weight or a family history of diabetes.

You are invited to participate in an important research study looking at preventing type 2 diabetes in young adults. This study is being conducted by Loughborough University and the Leicestershire Diabetes Research Team.

I am enclosing an information sheet giving details of the study. If you would like to participate in the study, please complete and sign the enclosed reply slip *and* pre-screening questionnaire and return them to the STAND Research Team in the provided pre-paid envelope. The study team will then contact you directly to arrange an appointment.

If you feel that you would like further information please call the Diabetes Research Team on 01162047981, email emma.wilmot@uhl-tr.nhs.uk or tick the appropriate box on the provided form and someone from the STAND team will contact you.

If you do not wish to receive any further invitations to participate in this research please let us know by ticking the appropriate box on the enclosed form.

Yours sincerely

GP

I have read the information sheet provided and **would like to take part** in the STAND Study.

☐

I have read the information sheet and **would like to hear more about** the STAND Study

☐

Name: _____

Signed: _____ Date: _____

I would prefer my initial appointment to be at:

Leicester Royal Infirmary
Leicester General Hospital

☐
☐

Please include your telephone number and email, if you have one, so we can contact you with further information.

Tel: _____

Email: _____



Pre-Screening Questionnaire

<<Name:>>
<<Address>>
<<Address>>
<<Address>>

GP Practice (If applicable)

Practice No:
Practice address:
EMIS NO:

I have read the information sheet provided and would like to take part in the STAND Study.

Participants Information:

Title: Name:

Preferred Telephone Number:

Email:

Date of birth Ethnicity Sex F / M
Height (cms) Weight (kgs)

Do any of these apply (please circle all that apply):

Family history of diabetes or heart disease	Yes	No	Don't Know
Diabetes	Yes	No	Don't Know
Previous diabetes during pregnancy	Yes	No	Don't Know
Polycystic Ovarian Syndrome	Yes	No	Don't Know

I would prefer my appointments to be at:

Leicester Royal Infirmary ☐
Leicester General Hospital ☐

I would prefer my appointments to be on a:

Monday ☐
Wednesday ☐

Dates not available:

.....



PHASE 3
Project STAND Randomised Controlled Trial:
PARTICIPANT INFORMATION SHEET

Professor Stuart Biddle Professor of Exercise and Sport Psychology, Loughborough University

Professor Melanie Davies Professor of Diabetes Medicine, University of Leicester and University Hospitals of Leicester NHS Trust

Professor Kamlesh Khunti Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester

Dr Emma Wilmot Clinical Research fellow, University Hospitals of Leicester

Dr Charlotte Edwardson Research Project Manager, Loughborough University

Title of project:

STAND (Sedentary Time AND Diabetes)

Invitation to participate:

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it involves. This information sheet is designed to help you decide whether you would like to participate in this study. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Why have you chosen to invite me – can anyone take part?

You may be one of the many people who are at risk of developing diabetes in the future. If you are aged 18-40 years with a family member (mother, father, brother or sister) with diabetes or heart disease, if you have had gestational diabetes, polycystic ovarian syndrome or your body weight is above the "normal" range then you may be eligible to take part in this study. In order to take part we also need you to have a good grasp of spoken English because this study is designed around an educational programme which will be delivered in English. In addition, if you are taking steroid medication for any long-term medical complication you may not be eligible to take part.

What is the purpose of the study?

The number of people with Type 2 diabetes is increasing dramatically. Type 2 diabetes used to be a condition older people developed. Now, more and more young people are starting to develop this condition. Our research team is interested in developing new and exciting ways to prevent diabetes. There is increasing evidence which suggests that prolonged sitting time (sedentary time) may actually increase the risk of diabetes. We are keen to find out whether reducing the amount of time people spend sitting reduces their risk of diabetes. This study is designed to answer this question.

Do I have to take part?

It is up to you to decide; participation is voluntary. We will describe the study and go through the information sheet. We will then ask you to sign a consent form to show that you have agreed to take part. You will be given a copy of the signed consent form. You are free to withdraw at any time without giving a reason. The treatment and standard of care you receive from the NHS will not be affected if you decide not to take part or to withdraw.

What will happen to me if I take part?

This study will last for 1 year and we will meet up with you at the start of the study, after 3 months and at the end of the study at 12 months. At the first visit you will be invited to visit the diabetes research team at a local venue and this visit will take around 3 hours. You will have the chance to meet the friendly members of our team, and to ask any questions you might have before signing our consent form.

When we meet you, we will record information about your medical history, any tablets you take and any family history of any medical conditions. We will check your blood pressure, weight, height and waist measurement. Blood tests will be taken. You will then be given Lucozade to drink and your blood tests will be repeated after 2 hours. These blood tests help us assess your risk of diabetes. As such, you will be asked to fast for this visit (water only from midnight the night before).

As part of the research study, we would also like to look at some important genes in your blood; however we understand this is a sensitive issue and we need to stress that these tests are optional and we have to ask for your consent separately for this. We will store the samples in our secure freezers for up to 10 years, after which time we will destroy them. All stored samples will be marked with an identification code and any genetic testing we do will be undertaken in an anonymous way. This will not affect anything personal to you in the future, such as life insurance. When you donate your samples you will be "gifting" them to us. If you are happy for us to take and store these extra samples then you will have to sign a box on the consent form. If you prefer not to have these samples taken, this does not affect your participation in the study.

During the 2 hour wait between blood tests, you will be asked to complete some questionnaires. We will also use this time to introduce the activity monitors used in the study, known as the 'Actigraph' and 'ActivPAL'. These small devices are worn on your waist and thigh and record your movement. We will demonstrate how to use the device and provide written instructions. After this study visit we would like you to wear the device for 10 days. We do this to assess how active you are and how much time you spend sitting. Once you have worn the device for 10 days, it is returned to us in the post. Once

your 2 hour blood test has been taken you are free to leave. We will send a copy of your blood results to your GP.

What happens next?

Taking part in the study involves being randomly entered into one of two study groups. The groups will be randomly selected (a bit like tossing a coin), so you cannot choose which group you are in. You will *not* know which group you are in before consenting to take part in the study.

Group 1 is what we call the 'control' group. If you are in this group, you will receive some useful leaflets informing you about your risk of type 2 diabetes and about how exercise and sitting less can be used to reduce this risk. At the end of the study period we will offer you the chance to attend the same 3 hour interactive workshop that is being given to Group 2 (see below).

Group 2 is the education group. If you are randomly assigned to be in the education group, we will invite you to the 3 hour STAND (Sedentary Time ANd Diabetes) group interactive workshop. At this visit two educators will deliver an interactive seminar focusing on what it means to be at-risk of diabetes and the impact of prolonged sitting on diabetes risk. During this visit we will discuss your blood results with you and calculate your individual diabetes risk. We will discuss ways of reducing your risk, one of which is reducing sitting time. You will also be told about the ongoing support that the research team is providing to help you reduce the time you spend sitting. During the next year you will be in regular contact with a diabetes healthcare professional with a wide range of resources to help you.

At the end of the interactive workshop you will be given full instructions on how to use a device which will let you monitor how much time you spend sitting. This will let you set goals to help you reduce the time you spend sitting. It is our hope that this reduction in sitting time will reduce your risk of diabetes.

If you are in the education group, in addition to the follow up study visits at 3 and 12 months, we will make contact with you via telephone after 3 months to specifically discuss how you feel you have progressed – have you managed to reduce your sitting time? If not, what barriers are there in the way of doing this?

Regardless of which group you are in at 3 and 12 months, we will ask you to visit us for a further fasting, 2 hour glucose blood test as described above. These help us keep an eye on your diabetes risk and your general well-being. During these visits we will also take a blood sample to measure your cholesterol levels and some key hormones that we measured before. We will also measure your:

- Height
- Weight
- Hip and Waist Measurements
- Blood Pressure

We will ask you to complete a questionnaire at each visit, just as you did when you joined the study and we will ask you to wear the same small physical activity monitors for ten days after each visit.

Optional additional assessments

There are 36 slots available for study participants to have their body fat analysed using magnetic resonance and x-ray technology. These additional study measurements are optional – it is for you to decide whether or not you would like to have them done. The slots will be offered on a first come, first serve basis.

These extra study tests involve attending Glenfield Hospital (Leicester) to have the muscle and fat content of your body assessed by a dual energy X-ray absorptiometry (DEXA) scan and an abdominal magnetic resonance imaging (MRI) scan. These scans will give you and us a detailed picture of the amount of muscle and fat you have in your body. In particular these scans will be able to measure how much fat you have stored around your vital organs, such as your liver and kidneys. This type of fat is particularly harmful and is strongly linked to your future risk of both type 2 diabetes and heart problems. It is unlikely that these tests would pick up any abnormalities with your health, but in the unlikely event that this happened we would discuss the results with you directly and, with your permission, inform your GP. DEXA and MRI scans are routine clinical tests but carry a small risk. DEXA involves exposure to radiation. The level of radiation exposure is exceedingly small (20µSv per scan) in comparison to the natural background radiation we are all exposed to (approximately 3000 µSv per year). The same level of radiation exposure would be received during a 2 hour intercontinental flight from radiation arising in outer space. MRI scans can be of concern for individuals who are highly claustrophobic (uncomfortable in confined spaces) and may be unsuitable if you have certain medical conditions. Both scans require you to lie still for up to 30 minutes. It is important to stress that these scans are optional and will not affect your participation in the study. If you have these scans performed at the start of the study, we would like to invite you to have them repeated at 12 months, the end of the study.

What do I have to do if I want to take part in this study?

If you decide to take part in the study you will be asked to sign a consent form when you come for your first visit. You will be given a copy of the patient information sheet and a copy of the signed consent form to keep for your own records.

What are the possible benefits of taking part?

By taking part in the study you and your GP will find out information about your diabetes risk, your cholesterol, your thyroid and liver function from the blood tests. You are unlikely to directly benefit from participating in the study. The results of this study will be used to improve future assessment and care for patients like you who are at risk of developing Type 2 diabetes. The results of this study will also help inform future guidance on the activity levels required for health.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Data will be stored either in locked filing cabinets or in password protected databases which are only accessible by members of the research team. Any information about you which is disseminated will have your name and address removed so that you cannot be recognised from it. Information collected will not be used for any

other purpose than that explained here. Your GP will be informed that you are taking part in this study.

What are the side effects of any treatment received when taking part?

There are no known side effects, other than the possibility of a small amount of bruising from having bloods taken.

What are the risks of taking part?

Taking part involves minimal risk for you, just the inconvenience of taking the time to participate in the study. The aim of this study is to develop an understanding of the impact of sitting time on diabetes risk. This will allow us to develop a fuller understanding of the role of sitting time and its relation to health. This study itself may not be of direct benefit to you but it will contribute to the ongoing work aimed at the prevention of Type 2 diabetes.

The tests in the study are not designed for clinical diagnosis, but in the unlikely event that we may find an abnormality either with the scan or blood results (eg diabetes) this will be discussed directly with you. With your permission, we will pass this information to your GP and any relevant specialist(s) with the aim of organising prompt and appropriate investigation and treatment.

What if something goes wrong?

It is very unlikely that you will come to any harm during this study. However, if you do come to harm through your direct participation in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the patient information and liaison service (PILS) are available to provide independent help, advice and support. They can be contacted at:

Gwendolen House,
Gwendolen Road, Leicester, LE5 4QF. Telephone: 08081 788337

Your legal rights to claim compensation for injury where you can prove negligence are not affected.

Will my taking part in this study be kept confidential?

Absolutely. All information that is collected about you during the course of the research will be kept strictly confidential in secure locations within Leicester Royal Infirmary.

Will my GP be informed of my results?

Yes, your family doctor will be informed of all the results of the tests taken as part of this study. When the study stops your GP will become the main point of contact for any ongoing concerns you have about your risk of diabetes.

Will I get study and travelling expenses?

Parking charges and travelling expenses up to £25 per visit can be reimbursed. Each study visit takes 2-3 hours and we appreciate that you are giving up your own time to attend these study visits. As such we will provide £20 for each study visit (maximum £60 over three study visits) which involves blood sampling, as a token of appreciation for your contribution to the study.

What will happen to the results of the research study?

The results of the study may be published in a professional journal, but you will not be identified by name in any publications. You will be informed about the results of the study when it has finished.

Who is organising and funding the research?

This study is being organised and co-ordinated by the University Hospitals of Leicester Diabetes Research Group and Loughborough University. The funding is coming directly from the Medical Research Council (MRC).

Who has reviewed the study?

This study was reviewed by the Nottingham Research Ethics Committee.

Contact for Further Information

Thank you for taking the time to read this information sheet. The doctors involved in this study will be pleased to discuss any questions or concerns that you may have. If you have any further questions about this research please contact the team on 07580802570 or email us at STAND@uhl-tr.nhs.uk.



Chief Investigator: Professor Stuart Biddle BEd, MSc, PhD
Principal Investigator: Professor Melanie Davies MBChB, MRCP, MD, FRCP, Consultant Physician
Contact: Dr Emma Wilmut, MB ChB, B.Sc.(hons), MRCP, Clinical Research Fellow

Study ID Label

CONSENT FORM: Version 7 20/02/2012
Phase 3: Randomised controlled trial

Title of project:	STAND: Sedentary time and diabetes	
Chief Investigator	Professor Stuart Biddle	Please Initial Every Box
I confirm that I have read and understand the STAND Phase 3 randomised controlled trial participant information sheet dated 18/11/2010 (Version 5) for the above study and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.		<input type="checkbox"/>
I agree to be contacted during the study by text messaging (for reminders to wear the study devices and appointment reminders).		<input type="checkbox"/>
I understand that relevant sections of my medical notes and/or study data may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to access my records.		<input type="checkbox"/>
I agree to the research team contacting my GP after the study has ended to allow remote follow up.		<input type="checkbox"/>
I agree to be contacted about participation in other studies.		<input type="checkbox"/>
I agree to blood samples being taken for future genetic analysis.		<input type="checkbox"/>
I agree to having a MRI and DEXA performed.		<input type="checkbox"/>
I agree to information and data collected in this study about me to be shared with a commercial company (GE Healthcare). My personal details, however, will not be shared.		<input type="checkbox"/>

 Name of participant

 Date

 Signature

 Researcher

 Date

 Signature



University Hospitals of Leicester NHS Trust
Diabetes Research Unit
Leicester Royal Infirmary
Leicester
LE1 5WW
Emma.wilmot@uhl-tr.nhs.uk
Tel: 0116 2047981

«GP_Title» «GP_FirstName» «GP_LastName»
«PracticeName»
«Practice_AddressLine1»
«Practice_AddressLine2»
«Practice_Town»
«Practice_PostCode»

Date

Dear Dr «GP_LastName»

The following patient has enrolled in project STAND (Sedentary Time and Diabetes). They attended for an oral glucose tolerance test and other routine bloods on «StudyDate». The results are listed below:

Patient: «Title» «Forename» «Surname», «Address1», «Address2», «Address3», «Town», «County», «Postcode».

Date of Birth: «DateofBirth»

Weight: «Weight» kg BMI: «BMI» kg/m2 Blood Pressure: «Systolic»/«Diastolic» mmHg

Blood Results:

Total Cholesterol	Result «Total_Cholesterol» mmol/L
LDL Cholesterol	Result «LDL_Cholesterol» mmol/L
HDL Cholesterol	Result «HDL_Cholesterol» mmol/L
Triglycerides	Result «Triglycerides» mmol/L
Sodium	Result «Sodium» mmol/L
Potassium	Result «Potassium» mmol/L
Urea	Result «Urea» mmol/L
Creatinine	Result «Creatinine» umol/L
eGFR	Result «eGFR» mL/min
HbA1c	Result «HbA1c» %
Fasting Glucose	Result «Fasting_Glucose» mmol/L
2 hour Glucose	Result «2hour_Glucose» mmol/L
Bilirubin	Result «Bili» mmol/L
ALT	Result «ALT» mmol/L
Alk Phos	Result «Alk_Phos» mmol/L
TSH	Result «TSH»

Yours sincerely

Dr Emma Wilmot
Research Registrar, Diabetes & Endocrinology

STAND Phase 3 GP baseline results letter
V1 010910

«Title» «FirstName» «LastName»
«AddressLine1»
«AddressLine2»
«Town»
«County»
«Postcode»
Date



University Hospitals of Leicester NHS Trust
Diabetes Research Unit
Leicester Royal Infirmary
Leicester
LE1 5WW
Emma.wilmot@uhl-tr.nhs.uk
Tel: 0116 2047981

Dear «Title» «LastName»,

Results from the STAND Study

Appointment Date
Height: m
Weight: kg
Body Mass Index: kg/m²
Blood pressure: mmHg
Cholesterol: mmol/L
Fasting Glucose: mmol/L
2 hour glucose

Desirable Values

Body Mass Index:	Below 25kg/m ² Below 23kg/m ² if South Asian
Blood Pressure:	Below 140/85mm/Hg
Cholesterol:	Below 5mmol/L
Fasting Glucose:	Below 6.1mmol/L
2 hour glucose:	Below 7.8mmol/l

I would like to thank you for taking part in the STAND study and for attending your recent study appointment.

Your results and the normal ranges are listed above.

I would like to advise you that your glucose tolerance is completely normal; therefore, you do NOT have diabetes. Your GP has been sent a copy of the above results.

Yours sincerely,

Dr Emma Wilmot
Research Registrar, Diabetes & Endocrinology



Project STAND; control arm information

Introduction

This booklet is designed to:

- Explain what Type 2 diabetes is
- Look at risk factors for developing Type 2 diabetes
- Look at ways to prevent Type 2 diabetes

What is Type 2 diabetes?

Glucose comes from food and drinks that we consume. During digestion glucose is released into the blood stream. Some of this glucose gets stored in the liver but some stays in the blood stream to be used in the body's cells as energy.

To enter the body's cells glucose must go through a 'gate' in the cell wall. Insulin (a hormone produced in the pancreas) helps the glucose to enter cells where it can be used as energy so we can work, play and generally live our lives.

Type 2 diabetes develops when the body can still make some insulin, but not enough, or when the insulin that is produced does not work properly (known as insulin resistance). Because of this, the pancreas has to work harder to produce insulin. Over time the pancreas gets worn out and makes less insulin. As a result less glucose gets into the body's cells and it stays in the blood stream.

To summarise, Type 2 diabetes is a condition where the amount of glucose in the blood stream is too high because the body cannot use it properly. It is this extra glucose in the blood stream that blood tests for Type 2 diabetes look for.

What are the symptoms of Type 2 diabetes?

There are generally no symptoms associated with being 'at-risk' from developing Type 2 diabetes but those who go on to develop Type 2 diabetes will experience the following symptoms:

- Feeling tired - because the glucose is in the bloodstream and not in the body cells where it is needed for energy - and feeling sleepy, especially after food.
- Going to the toilet often to urinate, especially at night - this is the body's way of getting rid of too much sugar from the bloodstream.
- Feeling thirsty - this is because you are going to the toilet a lot.
- Having more infections.

Why am I 'at-risk', and what is my risk?

If you have one or more of the following risk factors you are 'at-risk' of developing Type 2 diabetes in the future. Tick all the boxes that apply to you.

Risk Factor	Tick
I have a mother, father, brother or sister with Type 2 diabetes	
I am overweight or obese	
I have high blood pressure, or take tablets for my blood pressure	
I have high cholesterol, or take tablets for my cholesterol	
I have had angina, a heart attack or a stroke in the past	
I had gestational diabetes when I was pregnant	
I am inactive (undertake less than 30 minutes of physical activity per day)	
I am a woman with polycystic ovary syndrome	
I have mental health problems (e.g. depression)	
I have a diet high in fat and low in fibre	
I have been told that I have 'impaired glucose tolerance' or 'impaired fasting glycaemia'	
I sit for long periods of time	

How many boxes did you tick? If you identified one or more of the above factors then you are 'at-risk' of developing Type 2 diabetes in the future. The more boxes you tick, the greater your risk.

Can I lower my risk?

It's useful that you have found out you are at-risk of Type 2 diabetes because by making small changes to your lifestyle now you can reduce your risk of developing the disease in the future. The sooner you make changes the greater your chance of reducing your risk of developing the disease and its complications.

You don't have to make huge changes to make a difference, you can make small changes that fit in with your current lifestyle. There are some things that we cannot change but by eating a healthy diet and particularly by being more physically active you can dramatically lower your risk of developing Type 2 diabetes.

How does being physically active help?

Physical activity is one of the simplest and most effective things you can do to improve your health. Those that engage in regular physical activity have half the risk of developing Type 2 diabetes compared to those who do no exercise.

Physical activity helps reduce the risk of developing Type 2 diabetes by making it easier for glucose to get into the body's cells to be used as energy. This means that less glucose remains in the blood.

Being active also helps you:

- Lose and maintain weight
- Improve mobility
- Reduce depression and stress
- Keep your bones, muscles and joints healthy
- Prevent heart disease
- Prevent high blood pressure

How much activity do I need to be doing?

In order to gain health benefits and reduce your risk of developing Type 2 diabetes in the future you need to be doing a minimum of 30 minutes of moderate intensity on most days of the week. The 30 minutes can be accumulated throughout the day in 10 minute chunks and can include such things as brisk walking, swimming, cycling, aerobics or everyday activity such as vacuuming the house, washing the floor, digging the garden or mowing the lawn, as long as these activities are done vigorously enough to make you somewhat breathless.

You don't have to go out and buy lycra shorts and run round the park! Aim to find something you enjoy and can fit in around your lifestyle. Be as active as possible as often as you can. Simple things like taking the stairs instead of using lifts is a good place to start.

There is also increasing evidence that reducing the time that you spend sitting can improve your health. Try to substitute sitting activities with activities which involve standing (eg standing to play computer games). This may lower your risk of diabetes and heart disease.

If you do start an exercise programme remember to always start slowly and gradually increase the intensity and length of your sessions over time.

Can increasing my activity levels be dangerous?

Doing moderate levels of activity like walking should not normally present a danger to your health. However if you have a history of heart disease or exercising makes you feel dizzy or gives you pains in your chest you should consult a doctor. If you plan to start doing vigorous forms of exercise that involve running or lifting heavy weights you should always consult your doctor before you start in order to rule out any underlying problems that may become exacerbated by vigorous activity.

Useful resources

You may find the following resources useful to find out more about Type 2 diabetes and the risk factors for developing the disease.

<http://www.leicestershirediabetes.org.uk/>

This is the website to help promote the Department of Diabetes and Endocrinology at the University Hospitals of Leicester NHS Trust as one of the UK's leading 'Centre of Excellence' in Diabetes and Endocrinology.

<http://www.ndep.nih.gov/am-i-at-risk/>

This is the website of the National Diabetes Education Programme. The NDEP is an American organisation that translates the latest science and spreads the word that diabetes is serious, common, and costly, yet *controllable* and, for Type 2, *preventable*.

<http://www.diabetes.org.uk/>

Diabetes UK is the largest organisation in the UK working for people with diabetes, funding research, campaigning and helping people live with the condition.

Diabetes Careline: 0207 424 1030

Diabetes UK Careline provides support and information to people with diabetes as well as friends, family and carers.

<http://www.drwf.org.uk/> Tel: 023 92 637 808

This is the website of the Diabetes Research and Wellness Foundation. DRWF is a registered UK charity whose long-term mission is to discover a cure for diabetes and in the meantime to support, advise and educate people living with diabetes and the general public.

<http://www.diabetesresearchnetworking.org/> Tel: 01865 857508

Diabetes Research Networking is an innovative new website packed with information about diabetes and diabetes clinical research.

<http://www.patient.co.uk/health/Diabetes-Type-2.htm>

Patient UK is a website that provides comprehensive information as provided by GPs and nurses to patients during consultations.

<http://www.nhs.uk/Conditions/Diabetes-type2/Pages/Introduction.aspx>

Information on Type 2 diabetes from NHS Choices including causes, symptoms, diagnosis, risks and treatment and with links to other useful resources.

Questionnaires

Short International Physical Activity Questionnaire

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**.

Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐

No vigorous physical activities



Skip to question 3

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**.

Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

☐

No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐

No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐

Don't know/Not sure

Marshall Sitting Survey

Please estimate how many hours you spend SITTING EACH DAY in the following situations: *(please write your answer)*

+

	On a WEEK day		On a WEEKEND day	
	Hours	Minutes	Hours	Minutes
While travelling to and from places				
While at work				
While watching television				
While using a computer at home				
In your leisure time, NOT including television (eg visiting friends, movies, dining out, etc.)				

Appendix Six: Publications related to work in this thesis

Peer reviewed publications (copies of articles are presented below in the listed order)

Wilmot EG, Davies MJ, Benhalima K, Yates T, Lawrence IG, Khunti K. Type 2 diabetes in younger adults: The emerging UK epidemic. Postgraduate Medical Journal. 2010 Dec;86(1022):711-8. Epub 2010 Oct 21.

Wilmot EG, Davies MJ, Edwardson CL, Gorely T, Khunti K, Nimmo M, Yates T, Biddle SJ. Rationale and study design for a randomised controlled trial to reduce sedentary time in adults at risk of type 2 diabetes mellitus: project stand (Sedentary Time ANd diabetes). BMC Public Health. 2011 Dec 8;11:908.

Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJ. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia. 2012 Nov;55(11):2895-905. doi: 10.1007/s00125-012-2677-z. Epub 2012 Aug 14.

Wilmot EG, Edwardson CE, Biddle SJH, Gorely T, Henson JJ, Khunti K, Nimmo MA, Yates T, Davies MJ. Prevalence of diabetes and impaired glucose metabolism in younger 'at risk' UK adults: insights from the STAND programme of research. *Diabetic Medicine* 2013 *in press*

Details of conference presentations

Oral presentations

Diabetes UK

Wilmot EG, Davies MJ, Leggate M, McCann G, Gorely T, Benhalima K, Yates T, Khunti K, Nimmo M. Type 2 diabetes in young adults: a high risk phenotype for future cardiovascular disease. Diabetes UK March 2011, A11.

Wilmot EG. Hot topics invited speaker: Type 2 Diabetes in the Young: Complications and co-morbidities. Diabetes UK March 2011.

Wilmot EG, Leggate M, Khan JN, Gorely T, Morris DH, Khunti K, Gray LJ, Singh A, Yates T, Nimmo MA, McCann GP, Davies MJ. Type 2 diabetes in young adults: an extreme phenotype with early cardiovascular dysfunction. Diabetes UK, March 2013.

North European Young Diabetologists meeting

Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJH. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. North European Young Diabetologists Meeting, Amsterdam, August 2012.

Association of British Clinical Diabetologists meeting

Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJ. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. ABCD national SpR meeting, London, November 2012.

East Midlands Endocrine meeting

Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJ. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. East Midlands Endocrine Society meeting, Nottingham, December 2012.

Poster presentations – international meetings

International Diabetes Federation

Wilmot EG, Edwardson CL, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJH. Sedentary time and its association with Type 2 diabetes, cardiovascular disease and mortality: systematic review and meta-analysis. International Diabetes Federation 2011, Dubai. Poster.

European Society of Cardiology Congress

Khan JN, **Wilmot E**, Davies MJ, Gorely T, Khunti K, Leggate M, Nimmo M, Singh A, Yates T, McCann GP. Detection of Subclinical Left Ventricular Dysfunction in Asymptomatic Young Adults with Type-2 Diabetes: A Cardiac Magnetic Resonance Study. European Society of Cardiology Congress, 2012.

Poster presentations – national meetings

Diabetes UK

Wilmot EG, Davies MJ, Leggate M, McCann G, Gorely T, Benhalima K, Yates T, Khunti K, Nimmo M. Type 2 Diabetes in young adults: a high risk phenotype for future cardiovascular disease. Diabetic Medicine 2011; 28 (suppl 1): P200.

EG Wilmot, CL Edwardson, SJH Biddle, T Gorely, J Henson, K Khunti, MA Nimmo, T Yates, MJ Davies. Prevalence of diabetes and impaired glucose tolerance in younger UK adults. Diabetic Medicine 2013

UK Society of Behavioural Medicine

Wilmot EG, Davies MJ, Khunti K, Yates T, Gorely T, Nimmo M, Edwardson CL, Biddle SJH. Reducing sedentary behaviour in young adults at risk of Type 2 Diabetes: Project STAND (Sedentary Time ANd Diabetes) methodology. UKSBM 6th Annual Scientific meeting, Leeds, December.

The published articles from Appendix 6 (pp. 261-287) have been removed from the electronic version of this thesis due to copyright restrictions. The unabridged version can be consulted at the University of Leicester Library.

Appendix Seven: Prizes and awards related to work in this thesis

- Winner, East Midlands Endocrine Society meeting where I presented my systematic review and meta-analysis, Nottingham 2012.
- Selected as one in four UK “International rising stars in Diabetes” for inclusion in the Sanofi Aventis international development programme (2011).
- National runner up at the “Excellence in diabetes” meeting. £3.3K awarded (2010).
- Awarded national Society for Endocrinology post graduate essay prize. Runner up, £250 awarded (2009).
- National runner up at the “Excellence in diabetes” meeting. £10K awarded (2009).

Society for Endocrinology Award winning essay: Get up, stand up!

Introduction

We all know that being active is good for our health. It makes us live longer and helps prevent us from developing diabetes and obesity. To prevent us becoming part of the “diabesity” epidemic we are supposed to do 30 minutes of exercise on at least 5 days of the week. However, less than half of us achieve this. I, for one, am guilty. I pay a large sum of money each month to allow me to attend a gym. How many times have I been this year? Once! I was therefore delighted when I stumbled across evidence of a new way to reduce my risk of obesity and diabetes which, thankfully, does not involve dragging myself to the gym on most nights of the week.

Obesity epidemic

We are in the middle of an obesity epidemic. Why is this? There are a number of reasons which include increasing food portion sizes, the availability of energy dense foods and less physical activity. However, there is now mounting evidence suggesting that the time that we spend sitting each day could be a key factor contributing to the obesity epidemic, independent of the amount of exercise we do.

Sitting opportunities

If we think about it, the opportunities for sitting in today's world are ubiquitous. Many daily activities are performed sitting – sitting at your desk at work, emailing, watching TV, drinking a glass of wine with friends. Think about a typical day. For many it may start with driving to work to sit at a computer all day, driving home again and then sitting in front of a computer or the television for most of the evening. Some of us will then go to the gym in an attempt to convince ourselves that we lead a “healthy lifestyle”. Worryingly, *even* if you do perform the recommended 30 minutes of exercise a day you may not be protecting yourself against obesity and diabetes. For instance, Dave goes to the gym and does a 30 minute work out on most evenings. During the day he works in an office, sitting at his desk for most of the time. Gary, on the other hand, does not “exercise”. He works in a supermarket stacking shelves. You may be surprised to find out that, due to the prolonged time Dave spends sitting each day, his risk of obesity, diabetes and heart disease is probably higher than Gary who does no “exercise” (1).

Sitting and calories

When we think about it in more detail, it is easy to understand why sitting puts us at risk of poor health. Dave, who works in his office typically uses

~700 calories during his working day, compared to Gary who uses up ~1400 calories by standing for most of the day (2, 3). Therefore when Dave goes to the gym every evening the 300 calories he burns off during a 30 minute jog do little to compensate for the 700 calories which Gary has already used. The large difference in calories used up is a reflection of the fact that we spend most of our day sitting. Standing up, in comparison to sitting, requires the activation of lots of different muscles to support our weight, so it is easy to see why the daily calorie expenditure of Dave and Gary is so different.

Historical aspect

We have been aware of the hazards of prolonged sitting for many decades. In the 1950s Morris compared sedentary London bus drivers with active bus conductors. He found that the bus drivers had twice the risk of a heart attack compared with the bus conductors, even when their trouser waist size was taken into account (4). Over the last 100 years our lifestyles have changed dramatically. We now live in a society designed to make life easier for us. We have cars, televisions, computers, washing machines, dishwashers, vacuum cleaners, drive through restaurants, televisions, escalators, lifts, motorised walk-ways...the list is never ending. Unsurprisingly these changes which allow us to be less active on a day to day basis, correlate with rising obesity rates (5).

Sitting and health

In the past researchers were unable to accurately record time spent sitting. They had to rely on individuals recalling what activity they had performed. New technology (accelerometers) now allow accurate recording of the activity we perform in our day to day lives. Recent studies using this technology have

shown that sitting time, remarkably, now accounts for 90% of our average day. Of more concern, the time spent sitting directly relates to your waist size, body weight and risk of diabetes. These risks exist despite the volume of exercise people do (6). When sitting time is analysed in more depth, it becomes apparent that breaking up the time spent sitting has a positive effect on waist size, weight and risk of diabetes, again independent of any additional exercise people do (7). It would seem logical that if we reduce our total time spent sitting and avoid sitting for long periods, we can improve health and reduce the risks of obesity, diabetes and heart disease.

Genetic advantage

However, having a job which involves sitting for prolonged periods does not have the same negative effect on health for everybody. It seems that some of us are genetically determined to be more active, even if we do sit in an office all day. For instance, take Katie and Claire. They work in the same office and eat similar diets. However, Claire is designed to move about more than Katie. Claire fidgets at her desk, jumps up to answer the door at any opportunity and outside of work she is always on the move. Katie, however, prefers to sit at her desk, drive home and relax horizontal on the couch after a hard day at work. Some may think Katie is simply lazier than Claire. However, studies of twins have shown that the “non exercise” activity we do is not only environmentally but also genetically determined (5). In a study sets of identical twins were overfed and not allowed to exercise. Some sets of twins gained lots of weight while other sets of twins did not. The explanation for this is that some of the twins moved around more than the others. To put this in context, when Claire and Katie go on holiday together, despite eating the

same amount Katie typically gains 5lbs while, annoyingly for Katie, Claire's weight remains stable. This is because in a state of calorie excess, Claire is "programmed" to expend the extra energy in non-exercise activity such as fidgeting, standing and generally mobilising more. Katie will need to work hard to catch up with Claire – this will involve being aware of the activity she is doing and trying to consciously increase it.

Susceptible individuals

Although some of us seem to be programmed to "protect" ourselves from sitting too much, the other consideration is that some individuals are more vulnerable to the harmful effects of sitting than others. If you have a family history of diabetes and spend long periods of time sitting still you may be further increasing your risk of developing diabetes in the future (8). In a study, bed rest had a worse impact on metabolism in those with a family history of diabetes compared with those who did not. This would suggest that it may be more important for people with a history of diabetes in their family to avoid prolonged periods of sitting if they want to reduce their risk of developing diabetes in the future.

Conclusion

Rates of diabetes and obesity are soaring. We know the benefits of physical activity. Unfortunately in today's busy society meeting the activity recommendations is not a realistic goal for all of us. Reducing the time we spend sitting may prove to be an alternative way to improve health – given the choice, would you prefer to go to the gym for 30 minutes or stand for an extra hour a day? Either way, if you want to reduce your risk of diabetes and obesity you need to be active. How you achieve this is up to you. It is clear

that the opportunities for sitting are everywhere. However, having read this article it is my hope that you will think twice each time the opportunity to sit arises. Researchers of sitting time are leading the way – at conferences to discuss this topic the audience are not in their seats where you would expect to find them, instead they stand at the edge of the room to listen to the lectures! I am going to follow their example. I am finally going to cancel my underutilised, expensive gym membership and instead focus my attention on standing up!

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Appendix Eight: Media interest in the publication related to

Chapter Four

The systematic review and meta-analysis presented in Chapter Four of this thesis attracted a lot of national and international media interest when it was published in Diabetologia. Some examples of this media interest are present here in Appendix eight. More detailed insight into the level of media interest in this work can be found by entering the terms “sedentary Wilmot” into Google which results in 217,000 hits, the large majority of which are related to this publication.

Radio interviews

- Russian World Service
- BBC radio Leicester
- Superhuman radio
- Band News Brazilian Radio (recorded and translated interview)

The example web pages from Appendix 8 (pp. 296-304) have been removed from the electronic version of this thesis due to copyright restrictions. The unabridged version can be consulted at the University of Leicester Library.

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