
Psychosocial work stressors and risk of type 2 diabetes: Effect, impact and mechanisms

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A thesis submitted for the degree of Doctor of Philosophy in Epidemiology
and Public Health

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Abstract

Background: As early as the 17th century diabetes was linked to psychosocial stressors, yet this association still remains elusive. The impact of psychosocial work stressors on diabetes is also unknown, as are the pathways involved.

Aim: To investigate the prospective effect and impact of psychosocial work stressors on incident T2DM and elucidate direct and indirect pathways in this association.

Methods: Prospective analysis (1991-2004) among 5895 Caucasian middle-aged civil servants free from baseline diabetes in the Whitehall II cohort study. T2DM was ascertained by an oral glucose tolerance test supplemented by self-reports over four consecutive waves of data collection. The demand/control/support and effort-reward imbalance models were used to assess psychosocial work stressors.

Results: Job strain (high job demands/low job control), iso-strain (high demands/low control/low work social support) and effort-reward imbalance (high efforts/low rewards at work) are associated with 60% to 2-fold higher risk of T2DM among women but not men. This effect is higher among obese and lower socioeconomic position individuals. An estimated 35-44% of T2DM cases are attributed to psychosocial work stressors among exposed women, while 10-15% of all cases in the study population are estimated to result from exposure to work stressors, assuming a causal association. Biological factors (obesity, HDL-cholesterol and markers of inflammation) explain 1/3 of the effect of psychosocial work stressors on T2DM.

Conclusions: The observed association between psychosocial work stressors and T2DM is internally valid, temporal and biologically plausible, thus most likely causal. The external validity is questionable however as the effect was observed among a very specific sample of white-collar, Caucasian female civil servants. Given the interaction with body weight status, reduction of psychosocial work stressors would offer some benefits in light of the huge impact of the growing obesity epidemic on T2DM. Even though cardiometabolic and inflammatory factors explain a substantial part of the psychosocial effect on T2DM, other novel mediating factors should be identified. These results should be confirmed by other studies, preferably experimental, with special attention on gender differences. Policies for reduction of psychosocial work stressors should be informed by findings from such studies.

Acknowledgments

First of all I would like to thank my PhD supervisors Dr. Eric Brunner, Dr. Tarani Chandola and Dr. Daniel Witte for their continuous and consistent supervision of this research project and their valuable feedback. In particular, I would like to thank: Eric Brunner for his expert guidance on the overall concept of the PhD, as well as the importance of self-discipline and constantly keeping an updated timeline; Tarani Cahndola for his patience and time devoted on this project, as well as the valuable feedback on issues from selection of variables to statistical techniques to thesis structure and much more; Daniel Witte for his valuable support at the beginning of my PhD especially for his help on statistical techniques, as well as for helping me settle in and get started with the project.

Secondly, I would like to thank all the people from the Whitehall II group that helped in this project. In particular, Annhild Mosdol and Tasnime Akbaraly for their help with the diet data. Adam Tabak for his help with the diabetes variables. Jane Ferrie and David Gimeno for their help with data analysis. Aida Sanchez for her consistent help with all the variables needed for the project. Jean Persaud and Stephanie Smith for their help with applications and conference grants. I would also like to thank all Whitehall II study participants for their participation in the study and contribution to scientific research.

A big thank you to all my colleagues in the PhD room, especially Laia, Mojtaba, Popie, Neal, Somaia, Heeba and Ali. Sharing the PhD experience is priceless. Laia things would not have been the same without your support. A big thanks to other people in the Department of Epidemiology and Public Health who supported me during the PhD. Sandy, Catherine, Hynek, Mai, Paola, Martyn, George thank you all.

Last but not least, I would like to thank my friends and family for supporting me all the way. Andrea, nothing would have been the same without your patience and continuous help and support during these 3 years.

Statement of Authorship

With this statement I confirm that I have written the current thesis and analysed all data presented. I have not been involved in data collection (1985-2004) of the presented data but I was involved in data collection in phase 9 (2008) of the Whitehall II study. Below is a list of publications and presentations from this research project.

Peer-reviewed papers:

1. **Heraclides A.**, Chandola T., Witte DR., Brunner EJ. Psychosocial Stress at Work Doubles the Risk of Type 2 Diabetes in Middle-Aged Women Evidence from the Whitehall II study. *Diabetes Care* 2009, 32 (12): pp.
2. **Heraclides A.**, Chandola T., Witte DR., Brunner EJ. Obesity Modifies the Effect of Psychosocial Work Stress on Incident Type 2 Diabetes: the Whitehall II study. *International Journal of Obesity* 2010 (ready for submission).
3. **Heraclides A.**, Chandola T., Witte DR., Brunner EJ. Direct and Indirect Pathways Between Psychosocial Work Stress and Type 2 Diabetes in the Whitehall II study. *International Journal of Epidemiology* 2010 (prepared for submission).
4. Chandola T., **Heraclides. A.**, Kumari M. Psychophysiological biomarkers of workplace stressors and health. *Neuroscience & Biobehavioral Reviews* 2010 (under review).

Abstracts presented in international conferences:

1. **Heraclides A.**, Witte DR., Brunner EJ. Psychosocial work stress increases risk of type 2 diabetes in women: The Whitehall II study. *European Diabetes Epidemiology Group conference 2008*. Elsinore, Denmark (oral).
2. **Heraclides A.**, Chandola T., Witte DR., Brunner EJ. Comparison of measures of central and general obesity in relation to type 2 diabetes risk during a 15-year follow-up: The Whitehall II study. *European Diabetes Epidemiology Group conference 2009*. Wageningen, The Netherlands (oral)

List of Abbreviations

AUC:	Area Under Curve
BMI:	Body Mass Index
BMR:	Basal Metabolic Rate
CHD:	Coronary Heart Disease
CRP:	C-reactive protein
CVD:	Cardiovascular Disease
EI:TEE:	Energy Intake:Total Energy Expenditure
ERI:	Effort-Reward-Imbalance
FFQ:	Food Frequency Questionnaire
HDL:	High density lipoprotein
HOMA-IR:	Reciprocal Index of Homeostasis Model Assessment
HR:	Hazard Ratio
IL-6:	Interleukin-6
LRT:	Likelihood Ratio Test
MET:	Metabolic Equivalent
NEFA:	Non-Esterified Fatty Acids
OGTT:	Oral Glucose Tolerance Test
PAL:	Physical Activity Level
ROC:	Receiver Operating Characteristic
SEP:	Socioeconomic Position
T2DM:	Type 2 Diabetes Mellitus
vWf:	von Willebrand factor
WHR:	Waist-Hip Ratio
WHtR:	Waist-Height Ratio
WII:	Whitehall II

Chapter 1: Introduction

Diabetes mellitus, a disease of impaired glucose metabolism, has a huge burden in developed societies increasing both morbidity and mortality. As early as the 17th century, physicians had linked diabetes to “prolonged sorrow” (Willis, 1971). Prolonged sorrow refers, in this case, to what is today called chronic psychosocial stress. Yet, the relation between psychosocial stress and risk of diabetes is an under-researched topic in contemporary epidemiology. Two lines of evidence highlight the importance of investigating the role of psychosocial stress in the development of diabetes. First, psychosocial stress has been linked to heart disease (Brotman et al, 2009), obesity (Brunner et al, 2007) and the metabolic syndrome (Chandola et al, 2006), conditions closely linked to diabetes. Secondly, psychosocial stress has been linked to increased glucose levels and worse glucose tolerance among diabetic patients (Bruce et al, 1992).

This project investigates the effect and impact of psychosocial work stressors on risk of type 2 diabetes mellitus (T2DM), as well as the mediating pathways involved among a cohort of middle-aged white-collar British civil servants; The Whitehall II (WII) study. This study provides an excellent platform for examining the association between psychosocial work stressors and diabetes incidence in a substantial occupational cohort of men and women. This introduction chapter provides a background on the pathogenesis, epidemiology and burden of T2DM, including an account of the main determinants and risk factors of the disease. After this, a theoretical framework linking psychosocial factors to cardiometabolic disease will be presented, followed by a description of psychosocial work stressors and the plausible mechanisms linking them to increased risk of T2DM.

1.1. Type 2 diabetes: epidemiology, burden and determinants

1.1.1 Description, epidemiology and burden of diabetes

Diabetes mellitus is a metabolic disorder characterized by high blood glucose levels and deficient insulin action and production. Insulin is released from β -cells in the pancreas and is responsible for signaling insulin-sensitive tissues, such as skeletal muscle and

adipose tissue, to absorb glucose. In non-diabetic individuals this mechanism lowers blood glucose post-prandially and maintains glucose levels at approximately 5 mmol/L (90 mg/dL) in the fasting state. There are three main types of diabetes: type 1 diabetes, which is recognized as an auto-immune condition affecting people in childhood and early adulthood; gestational diabetes, affecting women during pregnancy; and type 2 diabetes, closely linked to environmental factors and affecting mostly adults. Type 2 diabetes has two main characteristics: (i) increased insulin resistance; and (ii) failure of compensatory insulin secretion due to beta cell failure/dysfunction. It is estimated that around 90% of diabetes cases are T2DM cases.

Insulin resistance refers to the reduction of the efficiency of body tissues to respond to insulin. In insulin resistant individuals, normal levels of insulin do not have the same effect on glucose uptake in muscle, adipose and liver cells due to defective insulin signalling. Reduced insulin sensitivity results in elevated blood glucose levels (hyperglycaemia). To compensate for this reduced sensitivity, the pancreas is stimulated by the increased blood glucose concentrations to release more insulin resulting in elevated insulin levels (hyperinsulinaemia). This condition of elevated blood glucose and insulin levels can progress to T2DM when pancreatic β -cells are unable to produce sufficient insulin to maintain normal blood glucose levels (Adams et al, 1984; Fröjdö et al, 2009).

The current definition of diabetes used worldwide is a 2-hour plasma glucose (oral glucose tolerance test) reading of ≥ 11.1 mmol/l (200mg/dl) or a fasting plasma glucose reading of ≥ 7.0 mmol/l (126mg/dl) (WHO/IDF, 2006). An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes. The committee in a report published in Diabetes Care in July 2009, encouraged the use of HbA1c (glycated haemoglobin) for the diagnosis of diabetes (The International Expert Committee, 2009).

The World Health Organization (WHO) estimates that, based on the current definition, more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030 (Wild et al, 2004). In the UK, diabetes prevalence increased in men from 2.9% in 1994 to 3.3% in 1998, to 4.8% in 2003, to 5.6% in 2006. The prevalence increased among women from 1.9% to 2.5% and 3.6% to 4.2% respectively (Sporston & Primatesta, 2003).

A review of cohort studies assessing 2-hour blood glucose levels in relation to mortality, found that a blood glucose level in the diabetic range (≥ 11.1 mmol/L) was associated with a 1.5 to 2.5-fold higher risk of all-cause mortality (Sorkin et al, 2005) (appendix 1). The excess global mortality attributable to diabetes was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths (Roglic et al, 2005). The WHO estimated that in 2005, 1.1 million people died from diabetes, with half of these deaths occurring in people under 70 years old (WHO/IDF, 2004). Apart from increasing mortality, diabetes is a major risk factor for heart disease and stroke. Around 50% of people with diabetes die of cardiovascular disease (WHO/IDF, 2004). In addition to heart disease and stroke, diabetes is directly linked to several conditions, collectively referred to as diabetic complications. These long-term complications include, diabetic renal disease (leading to kidney failure), diabetic retinopathy (leading to blindness), peripheral neuropathy (with risk of foot ulcers and gangrene), and autonomic neuropathy (which contributes to erectile dysfunction and cardiac arrhythmia) (WHO/IDF, 2004). Also, diabetics usually suffer from poor wound healing.

According to a report published in 2008, the NHS is spending £1m an hour (10% of the NHS budget) in treating diabetes and its complications, a figure totalling to £9bn a year (www.diabetes.nhs.uk/news-folder). Therefore, prevention of diabetes has been authoritatively proposed as a promising approach to drastically reduce the huge burden resulting from treatment of the disease and its complications (American Diabetes Association and National Institute of Diabetes, Digestive and Kidney Diseases, 2002). A WHO report on the prevention of chronic diseases (WHO, 2003) suggests that the

enormous and escalating economic and social costs of T2DM make a compelling case for attempts to reduce the risk of developing the disease.

1.1.2 Social determinants, risk factors and risk markers

Here, the term determinant is used for sociodemographic characteristics linked to T2DM; for example educational attainment. The term risk factor is used for behavioural and biological factors, for which there is strong, consistent and biologically plausible evidence for an association with incident T2DM; for example obesity. If a factor has been linked to T2DM in the literature but evidence is inconsistent then it will be called a risk marker; for example inflammatory markers.

The latest Health Survey for England highlights the alarming increase in obesity and T2DM prevalence and confirms that diabetes is socially patterned, with the prevalence increasing with decreasing socioeconomic position in the UK (Sporston & Primatesta, 2003). Prevalence of T2DM in the lower National Statistics Socioeconomic classification (NS-SEC) category is 5% among men compared to 3.9% in the higher category. The corresponding prevalence among women is 2.3% vs. 4.6%. This inverse gradient is clearer in women than men. This phenomenon of higher disease prevalence with every step down the social hierarchy is referred to as the social gradient in health and disease (Marmot, 2006). Social determinants of T2DM include low socioeconomic position (Connolly & Kelly, 1995; Bhopal et al, 2002; Agardh et al, 2004; Kumari et al, 2004), low educational attainment (Leonetti et al, 1992; Mazuk et al, 2008) and social adversity in childhood (Lidfeldt et al, 2007; Maty et al, 2008).

Obesity is considered to be the most important modifiable risk factor for T2DM. Increased body fat appears to be critical, particularly when located centrally in the abdomen, in the development of T2DM (Chan et al, 1994; Colditz et al, 1995; Ford et al, 1997; Jeffreys et al, 2006; Wild & Byrne, 2006; Hartemink et al, 2006; Klein et al, 2007). In fact, it is widely accepted that the T2DM epidemic observed around the world is a direct consequence of the global obesity epidemic (Clark, 1998; Beller, 2000; Seidel,

2000). In 1974, an editorial in the *Lancet* titled ‘Infant and adult obesity’ identified obesity as “*the most important nutritional disease in the affluent countries of the world*” (Editorial, 1974). More than 30 years later, prevalence of obesity has increased sharply among adults, adolescents, and children and now affects developing as well as developed countries (Prentice, 2006).

Despite the strong association between obesity and T2DM, lean people can also develop T2DM and not everyone who is obese develops the disease (García-Estévez et al, 2002; Meneilly and Elahi, 2005). In addition to obesity, several other risk factors have been linked to increased risk of T2DM. Physical inactivity (Helmrich et al, 1991; Manson et al, 1991; Manson et al, 1992; Mayer-Davies & Costacou, 2001; Hu et al, 2003; Hu et al, 2004; Jeon et al, 2007) and an unhealthy diet characterised by high saturated fat intake and low intake of dietary fibre (Mann, 2002; Parillo & Riccardi 2004; Steyn et al, 2004) have been linked to higher T2DM risk. In addition, smoking (Willi et al, 2007) and non-moderate alcohol consumption (Koppes et al, 2005) have also been linked to T2DM risk.

Biomarkers linked to risk of T2DM are similar to those linked to cardiovascular disease (CVD), hence the generic term cardiometabolic risk factors. Among these, increased blood pressure (Mancia, 2005), high levels of triglycerides and low levels of HDL-cholesterol (Grundy, 1999; Sattar et al, 2008; Clemens et al, 2004) have all been shown to predict incident T2DM. The metabolic syndrome, a cluster of risk factors including central obesity, hypertension, an adverse lipid profile (high triglyceride and low HDL-cholesterol levels) and impaired glucose tolerance is a major risk factor for T2DM (Mihic & Modi, 2008). Other novel risk markers that have been linked to T2DM include inflammatory markers (acute-phase cytokines and adhesion molecules) such as C-reactive protein (CRP) and interleukin-6 (IL-6) (Pickup, 2004; Sattar et al, 2008). Even though these novel biomarkers have been linked to incidence of T2DM in epidemiological studies, their role in causation of T2DM remains in question (Brunner et al, 2008). The above cardiometabolic and inflammatory factors usually co-occur (cluster) and it is very likely that they also co-occur with adverse psychosocial characteristics. Recently, genetic markers have been identified, which are closely linked to development

of T2DM. Common variations in the FTO and the MC4R genes have been linked to increased risk of obesity (Fan et al, 2000; Hubacek et al, 2008; Freathy et al, 2008; Willer et al, 2009) and T2DM risk (Qi et al, 2008). In addition there are at least 18 known common gene variants associated with diabetes risk (Perry & Frayling, 2008) that relate mainly to insulin secretion, as well as some genetic influences on insulin sensitivity (Langenberg et al, 2009) and glucose levels (Prokopenko et al, 2009).

Apart from the determinants and risk factors described above, psychosocial factors (or stressors) gained extra attention during the last 2 decades, mainly in relation to CVD but also T2DM. The magnitude of the effect of psychosocial factors on T2DM risk is not established due to the limited number of studies investigating this association and in addition, prevalence of such stressors in the population is largely unknown, thus the impact of psychosocial factors in T2DM and its burden is also unknown. The next sections provide an account of psychosocial factors and explain their link with cardiometabolic disease and T2DM in particular.

1.2 Psychosocial stressors and cardiometabolic disease

Psychosocial factors refer to the social circumstances in which people live and work and which have the potential to affect people's psychological state. Adverse psychosocial factors which could potentially generate chronic psychological stress are referred to as psychosocial stressors (Selye, 1956).

Broadly speaking, the literature on psychosocial stressors and cardiometabolic disease originated from three distinct, but related, paths: (i) anecdotal evidence from physicians; (ii) the health inequalities literature; and (iii) the psychological/sociological literature.

1.2.1 Anecdotal evidence from physicians

The link between psychological stress and diabetes was first recognised by Thomas Willis, in 1689, who noted that stress seemed to precede the appearance of diabetes in

many of his patients and commented that “*nervous juice hurtful to other humours and prolonged sorrow appear to be important risk factors for diabetes mellitus*” (Willis, 1971). By the 19th century, the role of psychosocial stressors in the aetiology of diabetes had gained substantial popularity in the medical literature. Both Henry Maudsley and William Osler observed that diabetes was often preceded by sudden trauma (Maudsley, 1899; Osler, 1896). The latter commented that stress was particularly important in what he termed ‘diabetes of obesity’ (referring to type 2 diabetes), noting that “*In true diabetes (type 1 diabetes), instances of cure are rare. On the other hand, the transient or intermittent glycosuria met with in stout overfeeders, or in persons who have undergone a severe mental strain, is very amenable to treatment*” (Osler, 1896). Among his interventions for T2DM were rest and opiates.

1.2.2 The health inequalities literature

In the UK, from the mid 19th century the observation that morbidity and mortality was socially patterned was documented by William Farr. Farr noted that people from lower social classes died, on average, younger than people in the high social classes. The Acheson report, more than 100 years later, investigated the reasons for this health inequality (Acheson, 1998) and proposed the psychosocial explanation as one of the three models, along with the neo-materialist and the cultural/behavioural explanations. Supported by considerable evidence (Marmot, 2006), the psychosocial explanation theorizes that psychosocial stressors affect the lower social classes more than the higher.

Advocates of the psychosocial explanation of health inequalities have elaborated the notion that belonging to a low social class within a hierarchical society has the potential to generate feelings of subordination. Such perceptions elevate risk of cardiometabolic disease, including T2DM, through psychosocial pathways, making a large contribution to the health inequality observed in modern societies (Wilkinson, 2006).

1.2.3 The psychological/sociological literature

In 1977 the psychiatrist George Engel proposed the biopsychosocial model of disease as an alternative to the traditional biomedical paradigm with its clear division between mind and body (Engel, 1977). The biopsychosocial hypothesis is centred on the observation that the social environment has the capacity to elicit adverse psychological reactions and that repeated exposure to these has cumulative physiological impact.

The sociologist Johannes Siegrist proposed a theoretical framework linking psychosocial stressors to cardiometabolic disease. This framework theorizes that psychosocial stressors are a direct result of unsuccessful social exchange between the person and society, which has a strong potential to affect health (Siegrist, 1995). A person's continuous fulfilment of important psychological needs, such as a favourable sense of self-efficacy and of self-esteem, depends to a large extent on opportunities to share in core social roles which offer opportunities of performing and acting (self-efficacy) and of getting reward and positive feedback (self-esteem). It has been suggested that expectations of dignity, reciprocity and fairness in social exchange are rooted in evolutionary 'old parts' of the human brain, reflecting our heritage as social mammals (Cosmides & Tooby, 1992).

1.2.4 From the mind to the body

The theoretical psychosocial frameworks outlined in the previous sub-section gain credibility with the addition of the biological dimension. The perspective here is that biological pathways link exposure to psychosocial stressors to negative emotions and lastly to pathophysiological change and disease. Nancy Krieger introduced the concept of embodiment, referring to how people literally incorporate, biologically, the material and social world in which they live (Krieger, 2005). As far as psychosocial stressors are concerned, embodiment relates to the ability of negative emotions to activate or modify functioning of the autonomic nervous system and one or more neuroendocrine systems.

The effects of psychosocial stress on the body can be broadly grouped into direct and indirect. Direct effects refer to the mechanisms through which exposure to psychosocial

stressors *per se* leads to pathophysiological changes (the concept of embodiment mentioned above). Indirect effects refer to the mechanisms by which psychosocial stress influences health behaviours, which in turn affect health. The term psychoneuroendocrine activation is commonly used to describe this process.

1.2.4.1 Direct effects

Chronic activation of the ‘fight-or-flight’ response (acute stress response) is recognised as central in the translation of psychosocial adversity into pathophysiological burden in the body (Sapolsky, 1993). The acute stress response evolved in humans as a rapid response to the challenge of external, potentially lethal, but short-termed physical or psychological threats (Brunner and Marmot, 2006). The acute stress response involves activation of the main axes of neuroendocrine response, the sympathetic-adrenomedullary and hypothalamic-pituitary-adrenocortical (HPA) systems, which coordinate an array of metabolic and physiological changes. Activation of the sympathetic-adrenomedullary axis results in rapid release of adrenaline from the adrenal medulla and noradrenaline from sympathetic synapses produces cognitive arousal, sensory vigilance, bronchodilation, raised blood pressure, haemoconcentration and release of blood clotting proteins such as fibrinogen. The second, and less rapid, component of the stress response involves activation of the HPA axis, resulting in release of glucocorticoids, including cortisol. Glucocorticoids have many effects, including vigilance, profound suppression of immunity, increase in low grade inflammation and mobilization of glucose and fat from body stores into the bloodstream (Brunner, 1997).

The function of the acute stress response described above is to prepare for or maintain physical exertion. From an evolutionary perspective, people are today living in an environment in which, maybe for the first time in human history, the systems described above instead of being protective, they are harmful. The material and social environment has changed beyond recognition over the past 10 000 years and especially the last 200 years after the industrial revolution. The biology of modern humans however, has remained essentially the same as it was in those early humans that dared the trip out of Africa 60 000 years ago. In the modern day environment, physical threats are rare, but the

social organization of everyday life very frequently generates psychological demands and challenges, which have the potential to activate the acute stress response.

Chronic or repeated activation of the acute stress response is thought to lead to pathophysiological changes in the body, a condition referred to as allostatic load. Allostasis refers to the condition in which the body is forced to alter its normal physiology as a response of coping with an environmental insult. When this adaptive process is overworked or fails to shut down after the stressor, the body is said to be in a condition of allostatic load (McEwan, 1998). The sympathetic-adrenomedullary and hypothalamic-pituitary-adrenal stress axes, described above, with the release of catecholamines and glucocorticoids result in acute psychological arousal and energy mobilization, mainly through accelerated heart rate, increase in blood pressure, mobilization of body fat and glycogen and increase in production of pro-thrombotic and inflammatory molecules. Chronically increased levels of catecholamines and glucocorticoids could thus potentially lead to disturbances in heart rate, hypertension, hyperlipidaemias, hyperglycaemia, insulin resistance, visceral fat accumulation, over-activation of the blood clotting system and increase in low-grade inflammation, subsequently increasing risk of cardiometabolic diseases such as obesity, heart disease and T2DM.

1.2.4.2 Indirect effects

Indirect pathways could potentially link psychosocial stressors to disease through health behaviours. Chronic activation of the acute stress response could potentially alter neurotransmitter balance in the brain. In particular imbalances in brain concentrations of dopamine (neurotransmitter involved in motivation and reward) and serotonin (neurotransmitter involved in mood and appetite) could increase the salience of pleasurable or compulsive activities (Dallman et al, 2003), such as consumption of high fat/high sugar foods, avoidance of physical activity, high consumption of alcohol and smoking (McEwan, 1998; Siegrist, 2000; Dallman et al, 2003). These behaviours in turn increase the risk of cardiometabolic disease.

1.2.5 Empirical findings

1.2.5.1 Evidence from studies among humans

Findings for an association between psychosocial stressors and obesity, cardiometabolic and inflammatory factors were inconsistent and inconclusive among humans. This evidence came from observational studies however, where exposure to stressors was subjective and self-reported. A large body of evidence on humans from smaller-scale experimental studies suggests that exposure to psychosocial stressors activates the acute stress response with subsequent activation of the two main stress axes (see chapter 1) leading to neuroendocrine activation and pathophysiological changes in the body.

In a sub-sample of the WII study, experimental psychosocial stressors (stroop and mirror tracing tasks) resulted in both elevations in cortisol levels during the working day (Steptoe et al, 2000) and post-stress blood pressure recovery (Steptoe & Marmot, 2006), suggesting activation of the HPA axis, as well as delayed heart rate recovery (Steptoe & Marmot, 2006), suggesting activation of the sympathetic-adrenomedullary axis. A recent meta-analysis of 30-year evidence from small-scale studies looking at the role of cortisol in the stress response concludes that there is convincing evidence that cortisol levels are elevated from exposure to psychosocial stressors (Chida & Hammer, 2008).

Small-scale experimental studies provide evidence that individuals at risk of T2DM (obese and insulin resistant) show signs of higher baseline levels and abnormal feedback of cortisol (Rosmond et al, 2000; Steptoe et al, 2004; Pasquali et al, 2006), diminished brain serotonin levels resulting in abnormal cravings for carbohydrate-rich foods (Ashley et al, 1985), higher self-reported emotional eating (Dutch Eating Behavior Questionnaire) (Cox et al, 1998), and higher brain activation in brain regions involved in reward mechanisms (Wang et al, 2006). It is unclear however whether these neuroendocrine and behavioural abnormalities are determinants or consequences of obesity and insulin resistance.

In experimental studies aiming to investigate psychoneuroendocrine pathways in the development of T2DM, participants who had a flat, rigid day curve and poor feedback mechanism of cortisol also had central obesity, insulin resistance and hyperglycaemia (Bjorntorp et al, 1999). The authors concluded that the metabolic abnormalities mentioned above are a result of elevations in cortisol secretion, which in turn arise from abnormal activation of the HPA axis (Rosmond & Bjorntorp, 2000). In a study of monozygotic twins discordant for obesity, when genetic factors were identical, visceral fat accumulation was associated with increased psychosocial stress and concomitant hormonal changes (Marniemi et al, 2002). Evidence for a temporal association between HPA activation and central obesity comes from the Whitehall II, where impaired post-stress recovery of systolic blood pressure (an indicator of chronic HPA activation) predicted increases in WHR over a 3-year period and this was independent of baseline obesity and other covariates (Steptoe & Wardle, 2005).

A separate line of evidence which highlights the involvement of cortisol in T2DM risk, is the accelerated weight gain and insulin resistance among people with subclinical Cushing's syndrome (Tauchmanova et al, 2002), which is characterized by mild autonomous cortisol hyper-production without specific clinical signs of cortisol excess.

In the WII study, in a case-control analysis, 24-hour cortisol metabolites and catecholamines were higher among participants with the metabolic syndrome compared to matched controls (Brunner et al, 2002). In addition heart rate variability (an indicator of autonomic activation) was lower among participants with the metabolic syndrome, suggesting chronic activation of the acute stress response. The authors found that psychosocial factors accounted for 37% of the link between the metabolic syndrome and activation of the sympathetic-adrenomedullary axis and 7%-19% for activation of the HPA axis. The metabolic syndrome is characterized by glucose intolerance and is a major risk factor for T2DM, thus these findings support the notion that activation of the acute stress response precedes the development of T2DM.

A recent meta-analysis of studies looking at the effect of experimental stressors in increases in inflammatory markers concluded that the meta-analysed results provided strong evidence for increased levels of circulating IL-6 and marginal effects for CRP following acute stress (Steptoe et al, 2007). In addition, fibrinogen was also shown to increase after exposure to psychosocial stressors (Steptoe et al, 2003).

It should be noted here that the effects of acute experimental stress on glucose metabolism is very different to the effect of chronic psychosocial stress. Experimental stress involves subjecting individuals to conditions that they are unlikely to encounter in their everyday life. Acute experimental stress serves more to demonstrate that psychological stressors do indeed have the potential to activate the acute stress response and related cardiometabolic and inflammatory changes. It is however the chronic effects on stress which hypothetically impair glucose metabolism and have the potential to increase diabetes risk.

1.2.5.2 Evidence from animal studies

Walter Cannon was the first to experimentally test the involvement of psychosocial stressors in hyperglycaemia and diabetes using animal models. Cannon showed that cats confined in a holder and exposed to a barking dog (stressor) had steep elevations in blood glucose levels (Canon, 1941). Also evidence from the *ob/ob* mouse (an animal model of T2DM) suggested that chronic exposure to psychosocial stressors was related to increased accumulation of body fat, especially visceral, and insulin resistance (Surwit & Williams, 1996; Kuo et al, 2007). The most rigorous investigation on the pathways linking psychosocial stressors to cardiometabolic risk, and the kind of research more linked to humans, was done in primates. During the 1980s, several researchers started investigating the effect of social hierarchy and psychosocial stressors in relation to several cardiometabolic risk factors (Sapolsky, 1993, 2005). For example Robert Sapolsky investigated psychosocial stressors and cardiometabolic risk among wild baboons, while Carol Shively investigated the same associations in captive macaque monkeys. Findings from this field of research were striking and showed that primates that

were exposed to psychosocial stressors, such as a subordinate status or social environment manipulation such as sudden altering of social status or introduction of 'intruder' primates in a stable group were associated with higher levels of fibrinogen, lower levels of HDL and a faster atherosclerotic rate (Shively & Clarkson, 1994).

On the behavioural (indirect) pathway, studies mostly concentrated on the consumption of unhealthy diets and alcohol after exposure to psychosocial stressors. Animal evidence on the association between exposure to psychosocial stressors and alcohol has been inconclusive (Heilig & Thorsell, 2002; Sillaber & Henniger, 2004) but the association with food intake has been consistent. Kuo et al (2007) showed that introduction of a psychosocial stressor (an aggressive mouse) in mice activated psychoneuroendocrine pathways. This activation was inhibited however in the presence of a high fat/high sugar palatable diet, indicating an anxiolytic role of such foods. Dallman et al (2007) investigated exposure to psychosocial stressors in rats during the last decade and concluded that chronic stressor-induced elevations in glucocorticoids increase the salience of pleasurable or compulsive activities, especially the consumption of high fat/high sugar foods. Finally, evidence from a research group on macaque monkeys suggests that exposure to psychosocial stressors caused an adherence to an unhealthier diet comprising of high fat/high sugar foods. This pathway was partly explained by activation of the sympathetic nervous system (*Strawn et al, 1991*).

To summarise, both animal and small-scale experimental studies among humans support that there could be an effect of psychosocial stressors on T2DM, which is however not confirmed by epidemiological evidence yet.

The current study concentrates on psychosocial *work* stressors as the source of psychological strain and negative emotions potentially leading to T2DM. The reasons for choosing psychosocial stressors in the workplace, as well as the concepts of these work stressors are described below.

1.3 Psychosocial work stressors

Sociologists talk about different spheres of life, such as the work environment and the home environment and suggest that each individual is expected by the society to fulfill certain core social roles (Siegrist, 1998). These include the worker role, the partner/family member role and the civic role (Bartley, 2004). Being unable to fulfill any of these roles leads to unstable contact between the individual and the society, in the form of failed social exchange, which may in turn lead to chronic psychosocial stress (Bartley, 2004).

The centrality of the work role for well-being in midlife in contemporary societies is clear. Work provides the principal source of continuous income, and more than any other social dimension it defines people's social identity and social status. In addition the work environment offers opportunities of learning and growth, of success and satisfaction, and of participating in broader social networks. Therefore, having a job offers recurrent options of contributing and performing by meeting the demands at work (the potential of experiencing favourable self-efficacy), and it offers recurrent options of reward, gain, and belonging (the potential to experience favourable self-esteem) (Siegrist, 1998).

The nature of work has undergone profound changes during recent decades. These days, most jobs are characterized by mental and emotional demands rather than physical demands. Job instability and forced mobility are becoming more prevalent (Marmot et al, 2006) resulting in insecurity and tensions among employees. In developed societies people spend around half of their non-sleeping day (8 hours) at work. Given these, the psychosocial work environment has considerable potential to affect people's psychological state and health. Psychosocial work stressors operating over years and decades may give rise to continuous or repeated activation of the stress response, resulting in increased cardiometabolic risk (see sub-section 1.2.4). Psychosocial work stressors could therefore be a factor increasing incidence of T2DM in modern societies. Recognition of the work environment as an important potential source of psychosocial stress led, during the last three decades, to the development of several empirical models for assessment of psychosocial work stressors. The most comprehensive of these are: (i)

the demand/control or job strain model (Karasek, 1979; Karasek & Theorell, 1990), which was later supplemented by an extra dimension, work social support (demand/control/support model) (Johnson and Hall, 1988); and (ii) the effort-reward-imbalance (ERI) model (Siegrist et al, 1986; Siegrist, 1996).

1.3.1 The demand/control/support model

The questionnaire for assessing the demand/control/support model of psychosocial work stress (Job Strain Questionnaire) was developed to provide an integrating theoretical framework for psychosocial work characteristics appropriate for the entire workforce (Johnson and Hall, 1988; Karasek & Theorell, 1990). The job demands indicator was constructed to measure the aggregate of psychological stressors affecting work. The job decision latitude indicator was constructed to measure the working individual's potential control over job-related decision making. The work social support indicator was constructed to measure the individual's opportunity to socially interact at work (Johnson and Hall, 1988).

The job strain model provides a framework for assessing psychosocial stress at work and posits that people working in jobs that are simultaneously characterized by high demands and low control are at risk of stress-related ill health and disease. The iso-strain model is an extension of the job strain model based on the hypothesis that people experiencing job strain and who are simultaneously socially isolated carry even higher risk for disease. Job strain and iso-strain have been previously associated with several health outcomes including minor psychiatric disorder (Stansfeld et al, 1995), cognitive decline (Elovainio et al, 2009), heart disease (Belkic et al, 2004, Kivimaki et al, 2006), obesity (Brunner et al, 2007) and the metabolic syndrome (Chandola et al, 2006).

1.3.2 The effort-reward-imbalance model

The theoretical approach of the effort-reward imbalance model is focused on the notion of social reciprocity, a fundamental principle of interpersonal behaviour and part of the 'evolutionary old' grammar of social exchange (Siegrist, 1998). Social reciprocity is

characterized by mutual cooperative investments based on the norm of return expectancy where efforts are equalized by respective rewards. Failed reciprocity resulting from a violation of this norm elicits strong negative emotions and sustained stress responses in exposed people because it threatens this fundamental principle (Siegrist et al, 1986). Conversely, positive emotions evoked by appropriate social rewards promote well-being, health and survival. High ERI has been previously linked to several disease outcomes. A review on the association between ERI and disease outcomes showed that 8 out of 8 studies assessing the effect of ERI on incidence of heart disease found a positive association. In addition, 13 out of 15 studies found an association between ERI and CVD risk factors. Finally, 13 out of 15 studies investigating the association between ERI and psychological well-being found a positive association (van Vegchel et al, 2005). In addition in a meta-analysis by Kivimaki et al (2006) there was pooled estimate of 60% higher risk of heart disease among those exposed to a combination of high efforts and low rewards in the workplace.

1.3.3 Similarities and differences between the stress models

Both the demand/control/support and the ERI questionnaires were both developed to provide an integrating theoretical framework for psychosocial work characteristics appropriate for the entire workforce. The ‘job demands’ (job strain and iso-strain models) and ‘efforts at work’ (ERI model) indicators both measure the aggregate of psychological stressors affecting work. The differences arise in the second concept of each model. For the demand/control/support model, ‘job decision latitude’ measures the working individual's potential control over job-related decision making, as well as skill utilization. For the ERI model, the ‘rewards at work’ indicator measures positive feedback in the workplace, both material (i.e. salary; career opportunities) and psychological (i.e. job satisfaction; support from supervisors).

The two models are thus similar in that they are based on theoretically-derived questionnaires on psychosocial work characteristics capable of generating work stress, but differ on their theoretical framework. The job strain and iso-strain models theorize

that it is the combination of high demands (or efforts), low control and low social support (iso-strain model) that is more likely to generate psychosocial stress, while the ERI model theorizes that it is the combination of high efforts (or demands) and low rewards that is more likely to generate stress.

There is no evidence that these different models of work stress have differing effects on psychoendocrine activation and disease outcomes and thus they are treated as alternative models of work stress in this project.

There is limited and conflicting evidence relating to the association between the psychosocial work stress models described above and T2DM. In addition evidence on the excess risk and population impact associated with exposure to these work stressors is lacking.

1.4 Mechanisms linking psychosocial work stressors to type 2 diabetes

Proposed mechanisms linking psychosocial stressors to cardiometabolic disease were outlined in section 1.3. A description of psychosocial stressors at work was given in section 1.4. The current section describes how these mechanisms might specifically increase risk of T2DM.

Activation of the sympatho-adrenal stress axis, with subsequent release of catecholamines, can increase hepatic glucose output and circulating levels of non-esterified fatty acids (NEFA) as a means of elevating availability of metabolic fuels in case of fight or flight (McEwan, 1998). Elevated levels of NEFA, in the physiological range, can impair insulin secretion and may be toxic to the beta cell (Kashyap et al, 2003). Activation of the hypothalamic-pituitary-adrenal stress axis, with the subsequent release of cortisol, may interfere with insulin action. Cortisol is an insulin antagonist and hypercortisolaemia is linked with increased gluconeogenesis, lipolysis, mobilization of amino acids and central redistribution of adipose tissue. The consequences may include increased blood glucose, NEFA and triglyceride concentrations (Brunner et al, 1997). Therefore, increased cortisol exposure may result in hyperglycaemia and compensatory

hyperinsulinaemia, while beta cell function is compromised by raised circulating NEFA level.

If these metabolic processes are chronically active, the risk of T2DM is likely to increase. Consistent with this mechanism, prevalent metabolic syndrome is accompanied by simultaneous elevations of urinary cortisol metabolites and normetanephrine, and reduced heart rate variability, compared to healthy controls (Brunner et al, 2002).

Activation of these neuroendocrine stress axes may be enhanced in obese individuals, suggesting potential interaction between obesity and psychosocial stress in the causation of T2DM.

The second hypothetical pathway linking psychosocial stressors to T2DM is the indirect behavioural pathway described in sub-section 1.2.4.2. Adverse health behaviours, such as high sugar/high fat diet, physical inactivity, high alcohol consumption and smoking, which are hypothesized to increase under conditions of exposure to psychosocial stressors (Siegrist, 1998; McEwan, 1998), are linked to the pathogenesis of T2DM.

The hypothetical pathways linking psychosocial stressors to T2DM have been described, but a question remains. Do *work* psychosocial stressors lead to psychological strain and a chronic activation of the acute stress response, as the models of job strain/iso-strain and ERI suggest? The empirical association between psychosocial work stressors and psychological strain has been previously demonstrated in relation to depression, sleeping problems, exhaustion (Karasek & Theorell, 1990) and emotional ‘burnout’ (Siegrist, 1998), indicating that these hypothesized stressors do indeed generate psychological stress. Psychosocial work stressors have been associated with increased salivary cortisol (Chida & Steptoe, 2009), delayed post-stress recovery of blood pressure (Steptoe and Marmot, 2005) and decreased heart rate variability (Steptoe and Marmot, 2005), providing evidence that these factors activate the two stress axes and could potentially increase the risk of T2DM.

Evidence for an association between psychosocial *work* stressors and cardiometabolic risk mainly comes from the WII study. In a WII sub-sample, men experiencing low job control showed greater fibrinogen responses to acute stress than did those with high job control (Steptoe et al, 2003). Also, overcommitment at work, a component of the ERI model was associated with elevated cortisol levels and systolic blood pressure over the working day among men (Steptoe et al, 2004). Among teachers, job strain was associated with a heightened blood pressure response to uncontrollable stressors and a delayed recovery to baseline blood pressure (Steptoe et al, 1999). The authors of the latter study concluded that failure of participants with high job strain to show reduced blood pressure in the evening may be a manifestation of chronic allostatic load resulting from exposure to psychosocial work stressors.

This section provided an account for the potential of psychosocial work stressors to cause chronic psychological strain, which in turn activates the acute stress response and initiates a cascade of pathophysiological changes. Three broad research questions arise which would extend understanding of the links between work stress and type 2 diabetes risk.

1. Does exposure to psychosocial work stressors increase risk of T2DM after controlling for potential confounding factors among healthy individuals in a non-experimental setting?
2. If there is an effect of psychosocial work stressors on T2DM, what is the excess risk and population impact associated with the exposure?
3. Does empirical evidence support the proposed direct and indirect pathways linking psychosocial work stressors to T2DM in a non-experimental setting?

This thesis addresses these questions among a population of white-collar middle-aged men and women in the Whitehall II cohort study. The next chapter reviews empirical

findings in the literature on the effect and impact of psychosocial work stressors on T2DM and the hypothesized pathways involved.

Chapter 2: Literature review

Chapter 1 discussed the pathophysiology, burden and determinants of T2DM, provided an account of the role of psychosocial factors in disease processes and identified the plausible mechanisms through which psychosocial work stressors can increase the risk of T2DM. The current chapter presents empirical evidence on effect, impact and potential pathways between psychosocial work stressors and T2DM from epidemiological studies. This literature review comprises of two parts:

1. Systematic review of the literature on the effect and impact of psychosocial work stressors on T2DM.
2. Review of the literature on the association between: (i) work stressors and health behaviours, obesity, cardiometabolic risk factors and markers of inflammation (potential mediators); and (ii) these potential mediators and T2DM risk.

The first part of this literature review involves a systematic search for evidence on the effect and impact of psychosocial work stressors on T2DM. ‘Effect’ refers to the relative risk of T2DM comparing people exposed to psychosocial work stressors to people not exposed. ‘Impact’ refers both to absolute (excess) T2DM risk attributable to exposure to psychosocial work stressors among those exposed (attributable risk) and to the excess T2DM risk attributable to psychosocial work stressors in the whole population under study (population attributable risk).

The second part of the review utilizes a narrative approach. Systematic reviews of the effect of psychosocial work stressors on T2DM risk factors and the effect of these risk factors on T2DM are not the focus of this study and much of the considerable body of evidence on these topics has recently been reviewed.

2.1 Chapter aim and objectives

Aim:

To assess the evidence from epidemiological studies on the effect and impact of psychosocial work stressors on type 2 diabetes and the pathways involved

Objectives:

1. To perform a systematic search of Medline (1966 – 2009) for epidemiological studies (cross-sectional; case-control; cohort) on the effect and/or impact of psychosocial work stressors (job strain, iso-strain and ERI) on T2DM
2. To conduct a systematic review on the identified studies of the effect and impact of psychosocial work stressors (job strain, iso-strain and ERI) on T2DM
3. To perform a search of Medline (1966 – 2009) for literature reviews/meta-analyses that investigated the association between psychosocial work stressors (job strain, iso-strain and ERI) and potential mediators (health behaviours, obesity, cardiometabolic factors and inflammatory factors)
4. To perform a search of Medline (1966 – 2009) for literature reviews/meta-analyses that investigated the effect of potential mediators (health behaviours, obesity, cardiometabolic factors and inflammatory factors) on risk of T2DM
5. To conduct a narrative review of published reviews on the potential pathways (health behaviours, obesity, cardiometabolic factors, inflammatory factors) between psychosocial work stressors and T2DM

2.2 Systematic review on the effect and impact of psychosocial work stressors on type 2 diabetes

2.2.1 Methodology

2.2.1.1 Search strategy

The search strategy developed to identify studies that investigated the association between psychosocial work stressors (demand/control/support model and effort-reward imbalance model) and T2DM was based on a widely recommended method for conducting systematic reviews of observational studies (Stroup et al, 2000). The search strategy is presented in table 2.1.

A combination of keywords using the *AND* and *OR* operators was used for the identification of epidemiological studies (cross-sectional; case-control; and prospective). The limits were set to: (i) 'humans'; (ii) 'English'; (iii) 'title/abstract'. The Medline database was searched from 1966 to June 2009. A list of keywords (table 2.1) was used for identifying studies on the demand/control/support and ERI models of psychosocial work stress. Then, another list of keywords was used for identifying studies with T2DM as the outcome. Finally, a list of keywords was used for identifying epidemiological studies. These 3 searches were then combined to identify epidemiological studies looking at the association between the demand/control/support and ERI models and T2DM. Evidence from smaller-scale studies was discussed in the introduction chapter (chapter 10).

The same search was carried out in PubMed (1950-2009), PsycINFO (1872-2009) and Web of Science (1900-2009) to identify articles missed in the initial search. Manual searches of the bibliographies of retrieved articles were conducted to identify further articles on the association between the work stressors of interest and T2DM. MeSH terms were not used since there were no entries for the main exposure variable (psychosocial work stress).

Table 2.1 Search strategy and keywords used to identify studies on effect and impact of psychosocial work stressors on type 2 diabetes in Medline

Search terms	Returned articles
1. job demands	1142
2. job control	2514
3. work social support	3013
4. demand/control	5
5. demands-control	24
6. job strain	775
7. iso-strain	16
8. effort at work	3451
9. reward at work	453
10. effort-reward imbalance	153
11. psychosocial stress at work	662
12. work stress	8869
13. work characteristics	9584
14. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	25 879
15. type 2 diabetes	35 184
16. non-insulin-dependent diabetes	7198
17. #14 OR #15	40 955
18. epidemiolog*	119 849
19. population-based	39 082
20. cohort	112 043
21. case-control	41 710
22. cross-sectional	71 966
23. case-referent	514
24. #17 OR #18 OR #19 OR #20 OR #21 OR #22	339 715
25. #14 AND #17 AND #24	18

Table 2.1 displays the search strategy followed in Medline for identification of studies on the effect/impact of psychosocial work stressors on T2DM. The search returned 18 article abstracts.

2.2.1.2 Study selection

In order to identify the suitable studies from within the 18 articles identified the following inclusion criteria had to be met:

1. Psychosocial work stressors were analysed as main exposure variables.
2. The outcome of the study was prevalent or incident T2DM, *not* impaired glucose tolerance, HbA1c, insulin resistance, or the metabolic syndrome.
3. The analysis was conducted among at least 500 participants (Kuper et al, 2002).

2.2.1.3 Search results

After applying these inclusion criteria, 5 studies out of the 18 were identified that investigated the effect of psychosocial work stressors on T2DM. From the initial 18 studies, 6 were excluded as they investigated the effect of acute stress another 5 studies were excluded as they assessed blood glucose and/or insulin and/or HbA1c instead of prevalence/incidence of T2DM; and finally, 7 studies which treated psychosocial work stress variables as potential confounders/mediators in other associations (i.e. social class in relation to T2DM) and did not report the effect of these variables on T2DM, were excluded.

All of the 5 identified studies assessed the effect of psychosocial work stressors on T2DM but none investigated the impact of these stressors on T2DM. Further manual search in the bibliographies of the selected articles did not identify further studies.

The selected studies were assigned a quality score (Laupacis, 1994; Chida & Hammer, 2008) based on: (1) sample size and gender; (2) study design; (3) exposure assessments; (4) diabetes ascertainment; and (5) adjustments. Each study received a score from 0-2 on each component. Thus, the potential range of the quality score was 0-10. In more detail, the studies were scored in the following way:

1. **sample size and gender:**
 - sample $\geq 10\ 000 = 1$
 - both genders = 1
2. **study design:**
 - cross-sectional = 0
 - case-control = 1
 - prospective = 2
3. **exposure assessment:**
 - based on all/some items from the original questionnaires = 1
 - job strain and ERI score derived according to the original protocols = 1
4. **diabetes ascertainment:**
 - ascertained by an oral glucose tolerance test = 1
 - repeated ascertainment = 1
5. **adjustments:**
 - adjusting for major confounders (SEP, non-work stressors) = 1
 - *not* over-adjustment (*not* adjusting for health behaviours, BMI, cardiometabolic risk factors) = 1.

The breakdown and total quality score for the selected studies is displayed in table 2.2.

2.2.2 Systematic review results

This section presents and discusses the findings of the first part of the current literature review, which systematically searched for evidence on the association between psychosocial work stressors and T2DM. Table 2.2 shows the quality scores for of the identified studies (section 2.2.1.2). The main findings of the systematic review are presented in table 2.3.

Table 2.2 Quality score of studies on the effect of psychosocial work stressors on type 2 diabetes

Study (country)	Reference	sample size and gender	study design	exposure assessment	outcome ascertainment	adjustments	Total score
Whitehall II Study (UK)	Kumari et al, 2004	1	2	1	2	1	7
The Nurses' Health Study II (USA)	Kroenke et al, 2006	1	2	2	1	1	7
The Belstress study (Belgium)	Leynen et al, 2003	1	0	2	0	1	4
Stockholm Diabetes Prevention Program (Sweden)	Agardh et al, 2003	0	1	2	1	0	4
Vasterbotten Intervention Programme (Sweden)	Norberg et al, 2007	2	1	2	1	1	7

2.2.2.1 Main characteristics of identified studies

The first population-based epidemiological studies on the association between psychosocial stressors and T2DM were published in 2003. Table 2.3 summarizes the evidence from the 5 epidemiological studies (2 prospective; 2 case-control; 1 cross-sectional) on the association between psychosocial work stressors and T2DM. Four of the studies were conducted in Europe (Kumari et al, 2004; Leynen et al, 2003; Agardh et al, 2003; Norberg et al, 2007) and 1 in the US (Kroenke et al, 2006). One of the identified papers used data from the WII study (Kumari et al, 2004). The current project extends the analysis by Kumari et al (2004) in several ways (see chapters 7 and 10).

One of the studies had a cross-sectional design (Leynen et al, 2003). Two of the studies had a case-referent design, with their sample derived from two population based surveys (both in Sweden) (Agardh et al, 2003; Norberg et al, 2007). Two were prospective cohort studies (Kumari et al, 2004; Kroenke et al, 2006). Two of the studies analysed only women (Agardh et al, 2003; Kroenke et al, 2006). Data were available for men in the Stockholm Diabetes Prevention Program but the published paper (Agardh et al, 2003) was restricted to analysis among women due to a null effect among men (personal

communication with authors). These results were presented at the European Diabetes Epidemiology Group conference 2009, and the authors are preparing a new publication showing prospective findings on both men and women (personal communication).

Sample sizes ranged from 4821 in the Stockholm Diabetes Prevention Program to 62 574 in the Nurses' Health Study II. Participant age at recruitments ranged from 29 years (Nurses' Health Study II) to 60 years (Vasterbotten Intervention Programme). Overall the youngest cohort was that of the Nurses' Health Study II (29-46) and the oldest the Vasterbotten Intervention Programme (40-60). All five identified studies assessed the effect of the demand/control/support model, while only one of the studies assessed the effect of the ERI model (Kumari et al, 2004). The analysis from the Whitehall II study did not assess the job strain model as high demands/low control/low work social support (i.e. co-occurrence of these characteristics) but instead assessed the component measures individually. Of the 2 prospective cohorts, the analysis from the Whitehall II study had the longest follow-up (14 years compared to 6 in the Nurses' Health Study II). The number of T2DM cases identified by these studies ranged from 44 in the Stockholm Diabetes Prevention Program to 529 in the Belstress study.

Table 2.3 Evidence from studies on the effect of psychosocial work stressors on type 2 diabetes

Study (country)	Study sample (age)	Exposure	Follow-up (years)	Outcome	No. of events	Adjustments	Relative risk (95% CI) (maximally-adjusted RR)	Quality score	Reference st
Demand/control/support model									
Whitehall II Study (UK)	8287 men and women (35-55)	job demands; job control; work social support	14 (1985-1999)	incident diabetes (OGTT)	361	family history, age, SEP, exercise, smoking, alcohol, BMI, height, blood pressure, ECG abnormalities	MEN: demands: 1.1 (0.7-1.7) (1.1) control: 0.8 (0.5-1.2) (0.8) support: 0.8 (0.5-1.1) (0.8) WOMEN: demands: 0.6 (0.3-1.2) (0.5) control: 0.8 (0.4-1.6) (0.9) support: 1.2 (0.7-1.9) (1.1)	7	Kumari et al
The Nurses' Health Study II (USA)	62 574 women (29-46)	job strain	6 (1993-1999)	incident diabetes (self-reported)	365	family history, age, SEP, exercise, smoking, alcohol, diet, BMI, work characteristics, menopausal status, aspirin use	WOMEN job strain: 1.1 (0.8-1.5) (1.1)	7	Kroenke et al,
The Belstress study (Belgium)	21 378 men and women (35-59)	job demands; job control; work social support; job strain	n/a	prevalent diabetes (self-reported)	529	age, SEP, exercise, alcohol, BMI, WHR, hypertension, depression	MEN: demands: 1.1 (0.8-1.5) (1.0) control: 1.6 (1.2-2.1) (1.3) support: 1.2 (0.9-1.6) (1.0) job strain: 1.1 (0.9-1.5) (1.0) WOMEN: demands: 0.9 (0.5-1.7) (0.9) control: 2.1 (1.2-3.8) (2.2) support: 1.6 (0.8-3.2) (1.8) job strain: 1.9 (1.2-3.1) (1.9)	4	Leynen et al,
Stockholm Diabetes Prevention Program (Sweden)	4821 women (35-56)	job demands; job control; job strain	n/a	prevalent diabetes (OGTT)	44	family history, age, exercise, smoking, BMI, WHR	WOMEN demands: 1.0 (0.5-2.0) control: 2.1 (1.0-4.7) job strain: 2.1 (0.8-5.2)	4	Agardh et al,
Vasterbotten Intervention Programme (Sweden)	33 336 men and women (40-60)	job demands; job control; job strain	n/a	prevalent diabetes (OGTT)	191	age, SEP, BMI	MEN demands: 0.9 (0.6-1.5) control: 1.0 (0.6-1.6) job strain: 1.0 (0.5-2.0) (1.1) WOMEN demands: 1.0 (0.6-1.8) control: 2.1 (1.0-4.7) job strain: 2.8 (1.1-7.6) (3.6)	7	Norberg et al,
ERI model									
Whitehall II Study (UK)	8287 men and women (35-55)	job demands; job control; work social support	14 (1985-1999)	incident diabetes (OGTT)	361	family history, age, SEP, exercise, smoking, alcohol, BMI, height, blood pressure, ECG abnormalities	MEN: ERI: 1.7 (1.0-2.8) (1.7) WOMEN: ERI: 0.9 (0.4-1.9) (0.9)	7	Kumari et al,

Abbreviations: OGTT (oral glucose tolerance test); ECG (electrocardiogram); SEP (socioeconomic position); BMI (body mass index); ERI (effort-reward imbalance)

2.2.2.2 Summary of effect of psychosocial work stressors on type 2 diabetes

As mentioned in the previous sub-section, none of the reviewed studies investigated the impact of psychosocial work stressors on T2DM, leaving thus a big gap in knowledge on this issue. For this reason only findings on the effect of work stressors on T2DM are discussed below.

2.2.2.2.1 Demand/control/support model

In the WII study (Kumari et al, 2004), the components of the Job Strain Questionnaire (high job demands; low job control; low work social support) were not associated with incident T2DM in either men or women. A weakness of this analysis was that the psychosocial work stress models of job strain and iso-strain were not assessed in relation to T2DM. As discussed in the introduction (section 1.3), it is the combination (interaction) of high demands/low control (job strain) and high demands/low control /low work social support (iso-strain) that are hypothesized to generate psychological strain and thus cause disease.

In the Nurses' Health Study II (Kroenke et al, 2006) job strain (high demands/low control) was not associated with incident T2DM among middle-aged women. Diabetes was self-reported in this study, something that may have introduced information bias in the results by diluting any association between job strain and T2DM. In addition, a recent review on the effect of psychosocial work stressors on heart disease concluded that cohorts recruiting from a single occupation may underestimate any effect of psychosocial work stressors on disease outcomes, as variation in psychosocial work characteristics may be limited (Eller et al, 2009). Further, the young age of the Nurses' Health Study II cohort may provide a potential explanation for the lack of effect as the incidence rate of T2DM is relatively low in younger ages

In the case-control analysis from the Stockholm Diabetes Prevention Program among 4821 healthy Swedish women aged 35–56 years residing in five municipalities in Stockholm (Agardh et al, 2004), job strain was associated with 2-fold higher odds of

prevalent T2DM. The association was however not statistically significant after adjustment for socioeconomic position and BMI and the age-adjusted effect was not reported. Adjusting for BMI can be regarded as a case of over-adjustment if BMI is in the causal pathway between job strain and T2DM. In the same study there was also a 2-fold higher odds of prevalent T2DM among women with low job control.

In the other nested case-control study from the Vasterbotten Intervention Programme in northern Sweden conducted among 33 336 men and women, aged 40-60, job strain was associated with ~3-fold odds of T2DM in women but not in men (Norberg et al, 2007). This effect increased slightly after adjusting for other covariates (age, SEP and BMI). In addition, low job control was associated with a 2-fold increase in prevalent T2DM among women.

The cross-sectional association between components of the demand/control/support model and prevalent T2DM was assessed in the Belstress study in Belgium among 21 378 male and female workers, aged 35-59 years, working in a wide range of different occupations (Leynen et al, 2003). The findings of this cross-sectional analysis were consistent with the two case-control Swedish studies, showing an association between low job control and job strain and prevalent T2DM among women but not men. These effects remained robust to adjustment for other covariates (age, SEP, exercise, alcohol, BMI, WHR, hypertension, depression). As discussed for the other studies, adjustment for these behavioural and biological factors can be regarded as over-adjustment as these are in the causal pathway between psychosocial work stressors and T2DM.

2.2.2.2 Effort-reward imbalance model

The association between effort-reward imbalance and T2DM was assessed in the Whitehall II study (Kumari et al, 2004). T2DM incidence during 14 years of follow-up was 65% higher among men who experienced high ERI compared to those not exposed to ERI. No effect was observed among women. The effect among men was robust to adjustment for potential confounders (table 2.3). As discussed for the

demand/control/support model, treating health behaviours, BMI and cardiometabolic risk factors as confounders can be regarded as a case of over-adjustment. The paper by Kumari et al (2004) is unique among those reviewed in showing an effect of psychosocial work stressors among men. The 3 studies that investigated the association between the demand/support/control model and T2DM among both men and women (Leynen et al, 2003; Agardh et al, 2003; Norberg et al, 2007) found an effect among women but not among men.

Overall, the results of the 5 studies that investigated the effect of psychosocial work stressors on T2DM, suggest that for the demand/control/support model, the combination of individual components (high demands and low control) is associated with prevalent T2DM, but only among women. Job strain was associated to prevalence or incidence of T2DM in 3 out of 4 studies that investigated this association. From the individual components, low job control was found to have an effect in 3 out of 5 studies. None of the studies investigated the effect of iso-strain. One study investigated the effect of ERI on T2DM and found an effect only among men.

This systematic review summarized evidence from 5 epidemiological studies suggesting that there is a trend of higher T2DM risk among women with low job control and job strain. Studies which did find an effect of job strain on T2DM had a lower quality score (apart from Norber et al, 2007) than the study which did not find an effect (Nurses' Health Study II). In fact, no prospective evidence supports this association and this is a research gap that the current project aims to fill.

2.3 Literature review on the potential pathways linking psychosocial work stressors to type 2 diabetes

2.3.1 Methodology

2.3.1.1 Search strategy

In order to assess the evidence on mediating pathways, studies on the association between the potential mediators (health behaviours, obesity, cardiometabolic factors and inflammatory factors) and both the main exposure and outcome were sought. This search was therefore conducted in two parts: (i) identification of studies on the association between psychosocial work stressors and potential mediators; and (ii) identification of studies on the effect of potential mediators on risk of T2DM.

The search for articles was conducted according to table 2.1. For the first part of the literature search, the terms used for identification of studies on T2DM risk factors were the following:

- (1) diet; (2) food choice;
- (3) physical activity; (4) exercise;
- (5) alcohol consumption;
- (6) smoking;
- (7) health behaviours;
- (8) obesity; (9) adiposity; (10) overweight; (11) weight; (12) BMI; (13) waist-hip ratio;
- (14) WHR; (15) waist;
- (16) blood pressure; (17) hypertension;
- (18) blood cholesterol; (19) blood lipids; (20) triglycerides; (21) hypercholesterolaemia;
- (22) hyperlipidaemia; (23) hypertriglyceridaemia;
- (24) metabolic syndrome;
- (25) fibrinogen; (26) inflamm*;
- (27) cardiovascular risk factors; (28) metabolic risk factors; (29) cardiometabolic risk factors.

The outcome of this search was combined with the outcome of the search on psychosocial work stressors (table 2.1 search #14), with the limits set to ‘review’ and ‘meta-analysis’. The search returned 131 review abstracts.

For the second part of the literature search, the terms used for identification of studies on potential mediators (above) were combined with the search on type 2 diabetes (table 2.1 search #17) *AND* ‘risk *OR* rate *OR* effect *OR* prospective’. The limits were again set to ‘review’ and ‘meta-analysis’. The search returned 210 review abstracts.

2.3.1.2 Study selection

In order to identify the suitable reviews from the 351 identified, the following inclusion criteria were applied:

1. The risk factor of interest (e.g. smoking, obesity) was the main focus (for evidence on the association between psychosocial work stressors and potential mediators)
2. Incidence of diabetes was the main outcome (for evidence on the association between potential mediators and T2DM risk)
3. The review was on epidemiological studies (cross-sectional; case-control; and prospective)

2.3.1.3 Search results

After applying these inclusion criteria the following were identified:

- 4 reviews of the association between psychosocial work stressors and health behaviours
- 1 review of the association between psychosocial work stressors and obesity

- 4 reviews on the association between psychosocial work stressors and cardiometabolic risk factors
- 2 reviews on the association between psychosocial work stressors and inflammatory markers
- 5 reviews on the effect of health behaviours on T2DM
- 3 reviews on the effect of obesity on T2DM
- 3 reviews on the effect of cardiometabolic factors on T2DM
- 3 reviews on the effect of inflammatory markers on T2DM

Summing this up, gives 25 reviews that investigated either the association between psychosocial work stressors and potential mediators or the effect of these mediators on incident T2DM. Further manual search in the bibliographies of the selected articles did not identify further reviews. In order to include studies published after the identified reviews and due to the fact that a limited number of reviews were identified for some associations, the search was extended to include evidence from individual studies. Studies with a sample size of ≥ 500 (Kuper et al, 2002) and which had a prospective study design were selected. If no such studies were identified for a given association, studies with a cross-sectional design were selected. This search identified the following:

- 12 studies of the association between psychosocial work stressors and health behaviours
- 4 studies on the association between psychosocial work stressors and obesity
- 2 studies on the association between psychosocial work stressors and cardiometabolic risk factors
- 6 studies on the association between psychosocial work stressors and inflammatory markers

This sub-section presented the methodology for searching the literature and selecting the studies to be reviewed. The following sub-section presents and discusses the findings.

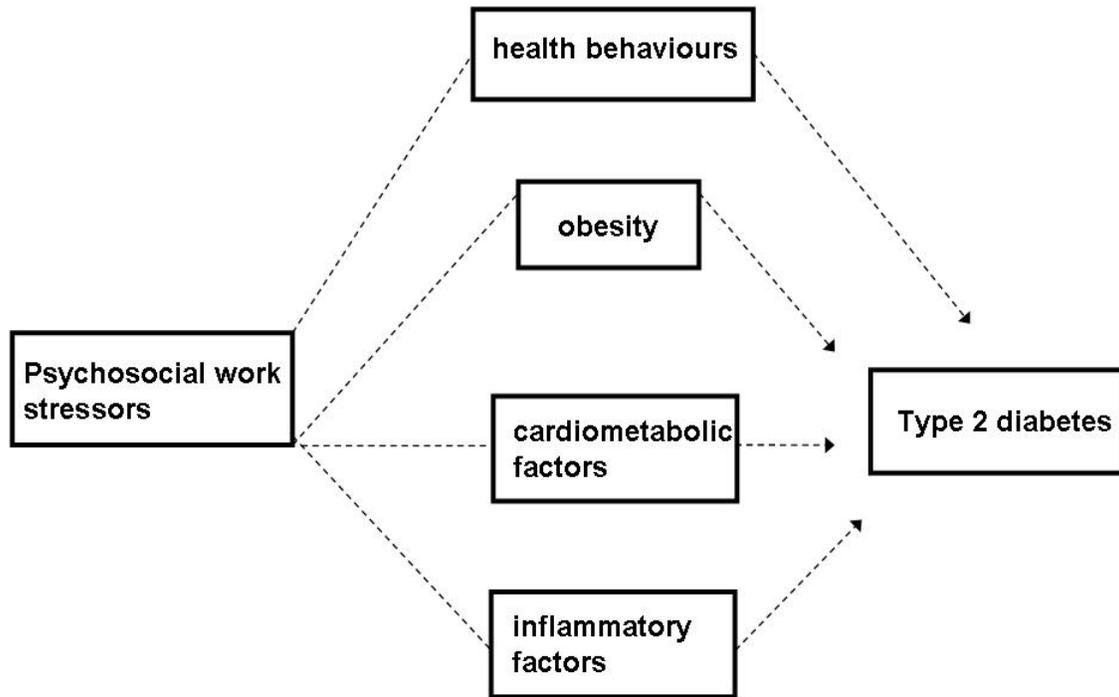
2.3.2 Narrative review results

The hypothetical pathways linking psychosocial work stressors to T2DM are displayed in figure 2.1. These pathways can be grouped into:

1. Pathway through health behaviours
2. Pathway through obesity
3. Pathway through cardiometabolic factors
4. Pathway through inflammatory factors

Even though these are displayed as distinct pathways in figure 2.1, in reality they could interact with each other (i.e. health behaviours affect obesity, which in turn affects cardiometabolic and inflammatory factors etc.) to increase T2DM risk. Investigation of evidence on the interactions between these pathways is not amongst the aims of the current chapter or the project in general.

Figure 2.1 Hypothetical pathways linking psychosocial work stressors to type 2 diabetes reviewed in the current literature review



2.3.2.1 Pathway through health behaviours

The sociologist Johannes Siegrist proposed a theoretical framework which involved psychosocial stress as a major determinant of health behaviours. His theoretical framework suggested that psychosocial work stressors may cause sustained negative feelings and tensions which could be alleviated by consumption of high fat/high sugar foods and alcohol, as well as by inactivity and smoking. This framework is supported by evidence from small-scale experimental studies and animal studies (Dallman et al, 2003). These behavioural risk factors are strongly linked to incidence of T2DM. Empirical evidence on the association between psychosocial work stressors and health behaviours is presented in table 2.4, while evidence on the association between health behaviours and T2DM is presented in table 2.5.

2.3.2.1.1 Psychosocial work stressors and health behaviours (table 2.4)

Most studies investigating the association between psychosocial work stressors and health behaviours concentrated on alcohol consumption (3 of 4 reviews) (table 2.4) . All 3 reviews on work stressors and alcohol assessed the demand/control/support model. The 4th identified review was on the association between ERI and multiple health behaviours. This was part of a larger review looking at general risk factors in relation to ERI. Due to the limited number of reviews on the association between psychosocial work stressors and health behaviours, individual studies that investigated this association were identified (N=11). From these, 1 study was on the association between psychosocial work stressors and diet, 2 on the association between psychosocial work stressors and physical activity, 1 on the association between psychosocial work stressors and smoking, 2 on the association between psychosocial work stressors and alcohol (not included in the 3 reviews) and the rest (N=5) were on multiple health behaviours.

2.3.2.1.1.1 Psychosocial work stressors and alcohol

Evidence from the 3 identified reviews on the association between psychosocial work stressors and alcohol consumption was mixed. One of the 3 reviews concluded on a consistent association between psychosocial work stressors and problem drinking (Trice, 1992). The other reported mixed findings of positive and null associations, but an apparent trend for a positive association between work stressors and heavy alcohol consumption (Frone, 1999). Finally, the third review concluded that the association between psychosocial work stressors and alcohol consumption was insufficiently studied (Ames & Janes, 1992). In the fourth identified review (van Vegchel et al, 2005) ERI was associated, among other health behaviours, to alcohol consumption in a cross-sectional study.

In contrast to earlier reviews (Trice, 1992; Frone, 1999; Ames & Janes, 1992), there was no evidence for an association between job strain and alcohol consumption in recent studies. Components of the demand/control/support model were not associated with alcohol consumption in a cross-sectional study that investigated unfavourable working

conditions in relation to diet, physical activity, alcohol consumption and smoking among 6243 employees in Helsinki (Lallukka et al, 2004). The same authors compared these results in Finland, with employees in the UK (WII study) and Japan (Japanese Civil Servants Study), again with no evidence for an association between components of the demand/control/support model and alcohol (Lallukka et al, 2008). Also, there was no association between job strain and drinking behaviours among 3099 US employees (Gimeno et al, 2009) and 40 851 Finish employees (Kouvonen et al, 2005b). In contrast, ERI was associated with problem drinking and higher alcohol intake in a cross-sectional analysis among 694 participants from Russia, Poland and the Czech Republic (Bobak et al, 2005). In these five individual studies, psychosocial work stressors were more comprehensively assessed compared to the earlier reviews.

2.3.2.1.1.2 Psychosocial work stressors and diet

In a prospective study conducted in 25 worksites in Oregon, US, 1110 participants took part in two health assessments aiming to examine work social support in relation to health behaviour change. Employees reporting low levels of work social support at baseline did not differ in terms of change in dietary fat intake compared to those reporting high levels of social support (Terborg et al, 1995). This study did not assess any other component of the demand/control/support model. In a cross-sectional survey in the US, job demands were positively associated with high fat intake in men but not in women. Job strain was not associated with fat intake (Hellerstedt & Jeffery, 1997). Components of the demand/control/support model were not associated with dietary intake in a cross-sectional study that investigated unfavourable working conditions in relation to health behaviours among Finish, British and Japanese civil servants (Lallukka et al, 2004; Lallukka et al, 2008). Job strain was positively associated with fat intake in men but not women in a cross-sectional survey in Japan (25 104 employees working in 9 companies) (Kawakami et al, 2006). In this Japanese study, social support at work was positively associated with both healthy (crude fibre and antioxidant vitamins) and unhealthy (total calories, cholesterol and saturated fat) nutrient intakes.

2.3.2.1.1.3 Psychosocial work stressors and physical activity

In a cross-sectional survey in the US, job control, but not job strain, was positively associated with exercise in both men and women (Hellerstedt & Jeffery, 1997). Job strain was associated with physical inactivity among men in the UK and women in Finland. In a cross-sectional study that investigated unfavourable working conditions in relation to diet, physical activity, alcohol consumption and smoking in Finland, the UK and Japan (Lallukka et al, 2004; Lallukka et al, 2008). Job strain increased the odds of low leisure time physical activity among 13 715 persons in a Swedish health survey (Wemme & Rosvald, 2005) but was only weakly associated with leisure-time physical activity among female and male Finish public sector employees (Kouvonen et al, 2005d).

2.3.2.1.1.4 Psychosocial work stressors and smoking

In a prospective study conducted in 25 worksites in Oregon among 1110 employees, those reporting low levels of work social support at baseline did not differ in terms of change in smoking compared to those reporting high levels of social support (Terborg et al, 1995). Job strain or iso-strain were not assessed. In a cross-sectional survey in the US, job demands were positively associated with both smoking status and smoking intensity in men, but only with smoking intensity among women. Job strain was only associated with smoking intensity and only among men (Hellerstedt & Jeffery, 1997). In a cross-sectional study that investigated unfavourable working conditions in relation to health behaviours among 6243 employees in Helsinki, job strain was only associated with smoking status among women (Lallukka et al, 2004). The same authors confirmed the weak and inconsistent association initially observed, but an effect was only apparent among Japanese men, in whom job strain was associated to current smoking (Lallukka et al, 2008). In a cross-sectional study among male middle managers high ERI was associated with a 4-fold risk of current smoking (Peter et al, 1998). Job strain and ERI were associated with smoking intensity among men and women, while ERI was associated with current smoking among Finish employees (Kouvonen et al, 2005a).

In a Finish study aiming to explore the association between job strain and the co-occurrence of adverse health behaviours (smoking, heavy drinking, physical inactivity and obesity) public sector employees, job strain was associated with higher odds of unhealthy behaviour co-occurrence. In addition, low job control among men, and high job demands among women were associated with a higher likelihood of co-occurrence of unhealthy behaviours. It should be noted however that this co-occurrence measure included obesity, which is investigated as a separate pathway by the current literature review (sub-section 2.2.2).

Overall, evidence from 4 reviews and 11 individual epidemiological studies on the association between psychosocial work stressors and health behaviours was mixed. The most consistent associations were observed between psychosocial work stressors and smoking and physical activity. The main reasons for the inconsistency of results are probably: (i) the inaccurate assessment of psychosocial work stressors in some of the studies; (ii) the wide variation in methods and variables used to assess health behaviours; and (iii) differences in attitudes towards health behaviours between different countries and populations.

2.3.2.1.2 Health behaviours and type 2 diabetes (table 2.5)

Due to the volume of evidence, this part of the literature review focuses only reviews and meta-analyses of lifestyle intervention studies and incidence of T2DM.

There were 5 reviews that summarized the effect of lifestyle intervention programmers on risk of T2DM, but only 1 commented on the results both quantitatively and qualitatively (Roumen et al, 2009). The latest of these reviews (Roumen et al, 2009) identified 10 individual lifestyle intervention studies. Common features of the lifestyle interventions were: (i) body weight loss $\geq 5\%$; (ii) healthy diet guidelines: carbohydrates=55% total energy, total fat<30%, saturated fat $\leq 10\%$ total energy, cholesterol <33 mg/MJ, protein 10-15% total energy; fibre 3g/MJ/day; (iii) 30 min of moderate physical activity per day at least 5 days a week.

All reviews agreed that there was strong evidence from lifestyle intervention studies that improvements in lifestyle can have a large and beneficial impact on T2DM risk. Recent data provide additional evidence on the long-term effects of healthy behaviours. Decrease in T2DM risk was especially efficient when the interventions included a combined diet and exercise program.

To summarise, there is mixed evidence on the association between psychosocial work stressors and health behaviours, with the most consistent associations found for physical activity and smoking. There is strong and consistent evidence for an association between health behaviours and T2DM. It is not clear, at least from the current literature review, whether health behaviours could act as mediators in the psychosocial work stressors-T2DM association.

2.3.2.2 Pathway through obesity

Obesity is recognised as the most important modifiable risk factor for T2DM. Excess body fat, especially if located intra-abdominally, has the potential to reduce insulin sensitivity eventually leading to insulin resistance and T2DM. Increasing evidence points to an important role of psychosocial stressors in the pathogenesis of obesity. The empirical evidence on the association between psychosocial work stressors and obesity is presented in table 2.6, while evidence on the association between obesity and T2DM is presented in table 2.7. Like in sub-section 2.2.1.2, the association between obesity and T2DM risk will only be briefly summarized due to the overwhelming evidence in the literature.

2.3.2.2.1 Psychosocial work stressors and obesity (table 2.6)

Emerging evidence suggests that exposure to psychosocial stressors contributes towards weight gain and risk of obesity through direct and indirect mechanisms. Even though overweight affects some 60% of the population in developed societies, the first evidence for an association between psychosocial work stressors and obesity only started appearing in the early 1990s.

A review of 10 cross-sectional studies summarized the epidemiological evidence on the association between psychosocial work stress and body weight up to 2004 (Overgaard et al, 2004a). The review showed little evidence of an association between psychosocial work stressors and BMI. Only weak positive associations were found with BMI in men. For WHR, two out of three studies showed a positive association in men, but these were attenuated after adjustment for education. No evidence for an association was observed in women. The review concluded that there was no evidence for an association between psychosocial work stressors and obesity and proposed that prospective epidemiological studies should be used to investigate any associations between exposure to chronic psychosocial stressors and weight gain.

Probably the strongest evidence for an effect of psychosocial work stressors on obesity comes from the WHI study from 2 papers published 2 years after the review by Overgaard et al (2004). Firstly, Kivimaki et al (2006) shed some light on the lack of robust associations between work stressors and obesity in epidemiological studies. These authors found evidence for a bidirectional effect of job strain on weight change in men during a 5-year follow-up, which dependent on baseline BMI. In the lowest baseline BMI quintile, high job strain and low job control were associated with weight loss during follow-up, whereas among those in the highest BMI quintile work stress was associated with subsequent weight gain. A year later, Brunner et al (2007) showed that iso-strain increased the risk of both general ($BMI \geq 30 \text{ kg/m}^2$) and central obesity (waist circumference $> 102 \text{ cm}$ in men, $> 88 \text{ cm}$ in women). These effects were largely independent of potential confounders.

In addition, a cross-sectional analysis in the Finnish Public Sector Cohort Study consisting of 45 810 male and female employees, individual-level as well as occupational- and organizational-level aggregated scores for work stress were associated with BMI (Kouvonen et al, 2005). In more detail, adjusting for SEP, higher job strain and higher ERI were associated with a higher BMI in men and women. In contrast, in a cross-sectional population-based survey conducted among working Australians in the state of Victoria, 1101 men and women (contacted by telephone from a random sample of

phone book listings), job strain and ERI were not associated with BMI (Ostry et al, 2006). A negative association between low reward and BMI was observed among women, while in men there were positive associations between high effort and high psychological demand with BMI.

Overall, cross-sectional studies tend to show null associations between psychosocial work stressors and obesity, something that is reflected by the lack of association concluded by the review of 10 cross-sectional studies (Overgaard et al, 2004). Evidence from prospective studies however (Kivimaki et al, 2006; Brunner et al, 2007), as well as from a large-scale cross-sectional study (Kouvonen et al, 2005c) points to a consistent and independent effect of psychosocial work stressors on risk of obesity. It should be mentioned however that 2 of the 3 studies showing an effect come from the WII study. Finally, evidence (again from the WII study) suggests that there may be special groups of individuals (i.e. overweight people) in whom the effect of work stressors on obesity is stronger.

2.3.2.2.2 Obesity and type 2 diabetes (table 2.7)

Due to the vast amount of publications on the associations between obesity and T2DM, this part of the review will summarise evidence from reviews and meta-analyses.

Hartemink et al (2006) in a meta-analysis of 31 population based cohort studies published from 1989 to 2005, investigated the prospective association between BMI and risk of T2DM. The authors found that an increase in 1 unit in BMI is associated with a 20% increase in T2DM risk. In a meta-analysis among 32 studies aiming to compare the risk associated with measures of central and general obesity (Vazquez et al, 2007), the pooled relative risks for incident T2DM per standard deviation increase in obesity measure were ~2 for BMI, waist circumference and waist-hip ratio.

A recent systematic review on the effect of obesity on several disease outcomes (Guh et al, 2009), reviewed 21 studies on the effect of obesity on T2DM. The authors concluded that the strongest association from all disease outcomes was the association between

obesity and T2DM risk. The meta-analysis revealed that obesity (\geq BMI30kg/m²) increased the risk of T2DM 7-fold among men and 12-fold among women. In addition, overweight was associated with 2.5-fold and 4-fold higher risk of T2DM in men and women respectively. Overall, 3 meta-analysis provide overwhelming evidence highlighting obesity as the most important risk factor for T2DM among men and women.

To summarise, there is growing evidence for an association between psychosocial work stressors and obesity and overwhelming evidence for a causal role of obesity in the pathogenesis of T2DM. Given this, the current review could conclude that some of the expected effect of psychosocial work stressors on risk of T2DM could be explained through obesity.

2.3.2.3 Pathway through cardiometabolic risk factors

Risk factors of cardiovascular disease have been established through decades of accumulated evidence. These include elevated blood pressure, adverse blood lipid profile (high triglycerides, high LDL-cholesterol, low HDL-cholesterol), hyperinsulinaemia and hyperglycaemia. It is widely accepted that these risk factors also increase the risk of T2DM. The association between psychosocial work stressors and these cardiometabolic risk factors is not well investigated in epidemiological studies.

2.3.2.3.1 Psychosocial work stressors and cardiometabolic risk factors (table 2.8)

Four reviews were identified on the association between psychosocial work stressors and cardiometabolic risk factors. Evidence generated from these 4 reviews is discussed in the current sub-section. In addition to recent individual studies assessing the effect of work stressors on clustering of cardiometabolic risk factors is also discussed.

2.3.2.3.1.1 Psychosocial work stressors and blood pressure

In an early meta-analysis of 5 cross-sectional studies (Pieper et al, 1989), job strain and its component measures were weakly and inconsistently associated with blood pressure. The relation of job control and systolic blood pressure was observed more consistent than

other associations. Job strain was not associated with blood pressure in any of the assessed studies. A review on the association between components of the ERI model and cardiometabolic factors, showed consistent evidence for an association between ERI and blood pressure (15 out of 17 showed a positive effect of ERI on either blood pressure or cholesterol) (van Vegchel et al, 2005). The results differed however between studies, as only some showed an association with blood pressure. Positive associations were also more consistent among men than women. In a review of 16 studies that investigated both job strain and ERI in relation to cardiometabolic risk factors, there was mixed evidence for an association between work stressors and blood pressure (Schnall et al, 1994). The associations between work stressors and blood pressure were less consistent compared to the associations with blood cholesterol and were more consistent among men than women. In a review that investigated both job strain and ERI in relation to blood pressure, no association between psychosocial work stressors and blood pressure reactivity or recovery was observed among 20 studies that investigated this association (Chida & Hammer, 2008b).

2.3.2.3.1.2 Psychosocial work stressors and blood lipids

A meta-analysis of 5 cross-sectional studies (Pieper et al, 1989), found that components of the demand/control/support model were weakly and inconsistently associated with blood cholesterol. Job strain was not associated with blood cholesterol in any of the studies reviewed. In contrast, a review on the association between components of the ERI model and cardiometabolic factors, showed a relatively consistent trend for an association between ERI and blood cholesterol across studies (15 out of 17 showed a positive effect of ERI on either blood pressure or cholesterol) (van Vegchel et al, 2005). Not all assessed studies showed an association between ERI and cholesterol however. The observed associations were more consistent among men than women. A review of 16 studies that investigated both the demand/control/support and the ERI models in relation to cardiometabolic risk factors, found mixed findings for an association between these work stressors and blood cholesterol (Schnall et al, 1994). The associations between work

stressors and cholesterol were more consistent however than with blood pressure. These associations were more consistent among men.

Two individual studies that add to the evidence from the above reviews, looked at the effect of iso-strain on clustering of cardiometabolic risk factors (Pelfrene et al, 2003; Chandola et al, 2006). The former assessed the association between iso-strain and the Framingham risk score and the latter the association with the metabolic syndrome. The two studies gave contrasting results however. Pelfrene et al (2003) found no evidence for an association between iso-strain and the cardiometabolic risk score, while Chandola et al (2006) showed a dose-response relation between iso-strain and risk of the metabolic syndrome, which was independent of other factors.

Overall, associations between psychosocial work stressors and individual cardiometabolic risk factors were weak and inconsistent, especially among women. Blood pressure was the factor less consistently associated with work stressors. None of the 4 reviews discussed above provided evidence for iso-strain. In an individual study, iso-strain was strongly associated with clustering of cardiometabolic risk factors (metabolic syndrome).

2.3.2.3.2 Cardiometabolic risk factors and type 2 diabetes (table 2.9)

The current literature review concentrates on evidence from 3 reviews on the effect of cardiometabolic risk factors on CVD and T2DM. Only the evidence on T2DM is discussed here. All 3 reviews summarize evidence on the association between blood pressure, blood cholesterol (LDL and HDL) and blood triglycerides and agree that there is strong evidence supporting a strong association between increased blood pressure, increased total and LDL-cholesterol and decreased HDL-cholesterol and risk of T2DM. The reviews agree that lifestyle factors such as weight gain, unhealthy diet and inactivity are responsible for elevating cardiometabolic risk factors to pathogenic levels and the pathways linking them to diabetes are through insulin resistance and impaired production of insulin from the pancreas.

To summarise, evidence on the association between psychosocial work stressors and individual cardiometabolic risk factors was weak and inconsistent. However, psychosocial work stressors were prospectively linked to the metabolic syndrome, a cluster of these factors. Cardiometabolic risk factors, as their name suggests, are a strongly linked with incident T2DM and this was confirmed by the current review. Based on this evidence, there is a possibility that some of the effect of psychosocial work stressors on risk of T2DM is mediated through cardiometabolic risk factors, especially blood lipids.

2.3.2.4 Pathway through inflammatory factors

This part of the review will refer collectively to inflammatory markers, as any cytokine or molecule whose levels are increased during the acute phase response. Strictly speaking some of these factors are not recognised as ‘inflammatory’ and may not be referred to as such in the literature. For example, markers such as fibrinogen, von Willebrand factor and factor VII are referred to both as coagulation and as inflammatory markers in the literature. CRP and IL-6 are amongst the most widely studied inflammatory markers for cardiometabolic disease. Inflammatory markers are recognised as novel risk factors for T2DM. Evidence on this association has not been consistent across studies however mainly due to the failure of some studies to adjust for the major confounder in this association, obesity. Small-scale experimental studies have shown that acute psychosocial stress increases levels of inflammatory markers. A small number of epidemiological studies have investigated these associations with psychosocial stressors.

2.3.2.4.1 Psychosocial work stressors and inflammatory markers (table 2.10)

The research on the association between psychosocial work stressors and inflammatory markers mostly concentrated on fibrinogen. Two reviews were identified which focused on psychosocial stressors in relation to coagulation markers.

2.3.2.4.1.1 Psychosocial work stressors and coagulation markers

Both reviews that investigated the association between psychosocial work stressors in relation to coagulation markers (fibrinogen, von Willebrand factor and factor VII) agreed that there was evidence, though not consistent, for a positive association. One of the two reviews concentrated only on the association between the demand/control/support model and fibrinogen and concluded that evidence from 9 epidemiological studies suggested that psychosocial work stressors based on this model may be linked to plasma fibrinogen concentrations and this relation was found to be more relevant in women than men (Theorell, 2002). The other review assessed evidence on the association between both the demand/control/support and ERI models and 3 coagulation markers (fibrinogen, von Willebrand factor and factor VII). This review concluded that there was some evidence that chronic psychosocial work stressors are related to a hypercoagulable state reflected by increased levels of pro-coagulant markers (von Känel et al, 2001).

Evidence on the association between work stressors and fibrinogen was also assessed from studies published after the two reviews discussed. In 3 cross-sectional studies which assessed the demand/control/support model in relation to fibrinogen, low job control was associated with higher fibrinogen levels among men (Clays et al, 2005; Hirokawa et al, 2008) but not women (Hirokawa et al, 2008; Alfredsson et al, 2002). In a prospective study which investigated the demand/control/support model in relation to several inflammatory markers, neither job strain nor iso-strain were associated with fibrinogen (Shirom et al, 2008). In an intervention study, among Whitehall II participants, low job control was associated with higher stress-induced fibrinogen levels in men but not in women (Steptoe et al, 2003).

2.3.2.4.1.2 Psychosocial work stressors and other inflammatory markers

No reviews were identified on the association between psychosocial work stressors and inflammatory markers other than those mentioned above. The individual studies identified mostly concentrated on CRP and IL-6. Evidence from these individual studies was mixed but there was a trend towards a null association. In two cross-sectional

studies, components of the demand/control/support model were not associated with either CRP or IL-6. In a prospective study investigating the demand/control/support model in relation to inflammatory markers, neither job strain nor iso-strain were associated with the markers assessed (CRP and white blood cell count) (Shirom et al, 2008).

Overall, associations between psychosocial work stressors and inflammatory markers were mixed and differed by gender. There was some evidence for an association between work stressors and fibrinogen but no associations were observed with CRP and IL-6. In an editorial, Theorell (2002) speculates that the mixed evidence for an association between psychosocial work stressors and inflammatory markers may be a result of isolating these markers and concentrating on associations between stressors and individual markers. He goes on to suggest that a cumulative measure of clustering of these markers may be more strongly linked to psychosocial stressors. This suggestion is supported by the evidence presented for cardiometabolic risk factors in sub-section 2.2.3 of this chapter, where individual cardiometabolic factors were weakly associated to work stressors but a clustering of these factors (metabolic syndrome) was strongly linked to work stressors (Chandola et al, 2006).

2.3.2.4.2 Inflammatory markers and type 2 diabetes (table 2.11)

The interest in the role of low-grade inflammation in the pathogenesis of T2DM started increasing during the last 20 years. For this reason good quality evidence from epidemiological studies is relatively new. The current literature review concentrates on recent evidence from 3 reviews on the effect of inflammatory markers on T2DM (Pradhan, 2007; Kolb & Mandrup-Poulsen, 2005; Pickup, 2004).

The 3 reviews summarize evidence on the association between CRP, IL-6, fibrinogen, Von Willebrand factor, factor VII, TNF- α and sialic acid and risk of T2DM. All 3 reviews agree in that there is growing evidence highlighting inflammatory markers as novel factors associated with T2DM risk. The identified reviews presented strong evidence supporting an association between increased levels of inflammatory markers and risk of T2DM from prospective epidemiological studies. All 3 reviews agree that

activated immunity may be the common antecedent of both T2DM and atherosclerosis, which probably develop in parallel. The pivotal importance of obesity and insulin resistance in the link between inflammation and T2DM is also highlighted.

It is still unclear however whether the specific biomarkers usually assessed in epidemiological studies (fibrinogen, CRP, IL-6 and others) do indeed contribute to the development of T2DM. A recent paper by Brunner et al (2008) showed, using Mendelian randomization, that genetic variants of CRP were not associated with insulin resistance and glycaemia, supporting thus that inflammation may play a causal role via upstream effectors rather than downstream markers.

To summarise, the current review found that evidence for an association between psychosocial work stressors and inflammatory markers is mixed and gender dependent, with the most consistent associations found with fibrinogen. In contrast, there is strong evidence suggesting a role of inflammation in the development of T2DM. Based on the current review it is unclear whether inflammatory markers could explain any of the association between psychosocial work stressors and T2DM risk.

Table 2.4 Evidence from reviews on the association between psychosocial work stressors and health behaviours

Behaviour	No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
Multiple health behaviours (alcohol, smoking)	2	Cross-sectional	yes	ERI	alcohol consumption; smoking	Evidence for an association between work stress and health behaviours	Y	van Vegchel et al, 2005
alcohol	39	cross-sectional; prospective	no	job demands; job control; job strain	amount of alcohol consumed; impaired control over drinking; heavy drinking; binge drinking	Mixed findings but a trend for a positive association between work stressors and heavy alcohol consumption	M	Frone, 1999
alcohol	unknown	cross-sectional	no	job demands; job control	amount of alcohol consumed; problem drinking; heavy drinking	Consistent association between psychosocial work stressors and problem drinking	Y	Trice, 1992
alcohol	unknown	cross-sectional	no	job demands; job control	amount of alcohol consumed; problem drinking; heavy drinking; high-risk drinking	Association between psychosocial work stressors and alcohol insufficiently studied	M	Ames & Janes, 1992
Multiple health behaviours (diet, exercise, smoking)	single study (N=3843)	cross-sectional	n/a	job demands; job control; job strain	smoking; exercise; dietary fat intake	job demands, job control and job strain were associated with some of the health behaviours (results depended on gender and work characteristic)	M	Hellerstedt & Jeffery, 1997
Multiple health behaviours (diet, exercise, alcohol, smoking)	single study (N=6243)	cross-sectional	n/a	job demands; job control; job strain	Diet; physical activity; alcohol consumption; smoking.	job demands, job control and job strain were only weakly associated with health behaviours (results depended on gender, work characteristic and health behaviour assessed)	M	Lallukka et al, 2004
Multiple health behaviours (diet, exercise, alcohol, smoking)	single study (N=11 680)	cross-sectional	n/a	Job strain	unhealthy food habits; physical inactivity; heavy drinking; smoking	job strain showed mostly weak and inconsistent associations with adverse health behaviours	M	Lallukka et al, 2008
Multiple health behaviours (exercise,	single study (N=42 239)	cross-sectional	n/a	Job strain	smoking; heavy drinking; physical inactivity	Job strain may be associated with the co-occurrence of adverse health behaviours (results	M	Kouvonen et al, 2007

alcohol, smoking)						depended on gender, work characteristic and health behaviour assessed)		
Multiple health behaviours (diet, smoking)	single study (N=1110)	prospective	n/a	work social support	dietary fat intake; smoking behaviour	social support at work did not predict future behaviour change.	N	Terborg et al, 1995
diet	single study (N=18 148)	cross-sectional	n/a	job strain; work social support	nutritional assessment for 17 nutrients	Job strain and worksite support were only weakly and inconsistently associated with nutritional intakes	M	Kawakami et al, 2006
physical activity	single study (N=13 715 men and women)	cross-sectional	n/a	job strain	low leisure time physical activity	Job strain increased the odds of low leisure time physical activity	Y	Wemme & Rosvald, 2005
physical activity	single study (N=46 573 men and women)	cross-sectional	n/a	job demands; job control; job strain	Leisure-time physical activity (MET-hours/week)	weak association between higher work stress and lower leisure-time physical activity	Y	Kouvonen et al, 2005d
alcohol	single study (N=3099men and women)	cross-sectional	n/a	job strain	three drinking behaviours (frequent, heavy and drinking and work)	No association between job strain and drinking behaviours	N	Gimeno et al, 2009
alcohol	single study (N=40 851 men and women)	cross-sectional	n/a	job demands; job control; job strain	heavy drinking (sex-specific cut-offs)	Stressful work conditions are not consistently associated with heavy drinking	N	Kouvonen et al, 2005b
alcohol	single study (N=694 men)	cross-sectional	n/a	job control; ERI	annual number of drinking sessions; mean dose of alcohol per drinking session; binge drinking (≥80 g of ethanol in one session at least once a week)	ERI associated with increased alcohol intake and problem drinking.	Y	Bobak et al, 2005
smoking	single study (N=46 190 men and women)	cross-sectional	n/a	job demands; job control; job strain; effort at work; reward at work; ERI	smoking status; smoking intensity	Positive associations between job strain and ERI and smoking (results depended on gender and the work stress model used)	Y	Kouvonen et al, 2005a

*Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.5 Evidence from reviews on the association between health behaviours and risk of type 2 diabetes

No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
10	intervention	yes	body weight loss; healthy diet; physical activity	incident T2DM	Lifestyle interventions are cost-effective and should be optimized to increase adherence and compliance	Y	Roumen et al, 2009
6	intervention	no	body weight loss; healthy diet; physical activity	incident T2DM	The present challenge is to translate the evidence into policies and practices that maximize the potential health benefits for the largest number of individuals.	Y	Samuel-Hodge et al, 2006
4	intervention	no	body weight loss; healthy diet; physical activity	incident T2DM	Four clinical trials using lifestyle interventions comprised of weight loss, physical activity, and diet have successfully prevented or delayed the onset of diabetes development in high-risk individuals	Y	Kriska et al, 2004
3	intervention	no	body weight loss; healthy diet; physical activity	incident T2DM	This body of evidence from randomized, controlled trials conducted in 3 countries has definitively established that maintenance of modest weight loss through diet and physical activity reduces the incidence of T2DM in high-risk persons	Y	Williamson et al, 2004
3	intervention	no	body weight loss; healthy diet; physical activity	incident T2DM	Several recent major clinical trials confirm that type 2 diabetes can be delayed or prevented in people at high risk	Y	Naravan et al, 2003

*Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.6 Evidence from reviews and individual studies on the association between psychosocial work stressors and obesity

No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
10	Cross-sectional	yes	job demands; job control; job strain	BMI; WHR	The reviewed articles were not supportive of any associations between psychosocial work stressors and either general or abdominal obesity	N	Overgaard et al, 2004
single study (N=3471 men and women)	prospective	n/a	job demands; job control; job strain	obesity (BMI≥30kg/m ²); central obesity (waist>102cm men, 88 cm women)	Prospective, population-based evidence that chronic work stress predicts general and central obesity	Y	Brunner et al, 2007
single study (N=7965 men and women)	prospective	n/a	job demands; job control; job strain	weight change	Differential effects of work stress on weight change deepened on baseline adiposity	Y	Kivimaki et al, 2006
single study (N=1101 men and women)	Cross-sectional	n/a	job demands; job control; job strain; effort at work; reward at work; ERI	BMI	Gender differences in both exposure to psychosocial working conditions and associations with BMI	N	Ostry et al, 2006
single study (N=45 810 men and women)	Cross-sectional	n/a	job demands; job control; job strain; ERI	BMI	Weak association between work stress and BMI	Y	Kouvonen et al, 2005c

*Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.7 Evidence from reviews on the association between obesity and risk of type 2 diabetes

No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
21	cross-sectional; prospective	yes	overweight; obesity	incident T2DM	Both overweight and obesity are associated with the incidence of T2DM	Y	Guh et al, 2009
32	cross-sectional; prospective	yes	BMI; waist; WHR	incident T2DM	Although the clinical perspective focusing on central obesity is appealing, further research is needed to determine the usefulness of waist circumference or waist/hip ratio over BMI.	Y	Vazquez et al, 2007
31	cross-sectional; prospective	yes	BMI	incident T2DM	Strong effect of BMI on incident T2DM, which is non-linear however	Y	Hartemink et al, 2006

*Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.8 Evidence from reviews and individual studies on the association between psychosocial work stressors and cardiometabolic risk factors

	No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
Multiple cardiometabolic factors (cholesterol, blood pressure)	5	Cross-sectional	yes	job demands; job control; job strain	cholesterol; systolic and diastolic blood pressure	Psychosocial aspects of work, in particular job control, may be related to some cardiovascular risk factors. Job strain was associated with none of the risk factors. None of the psychosocial stressors was linked to blood pressure.	M	Pieper et al, 1989
Multiple cardiometabolic factors (cholesterol, blood pressure, haemostatic)	16	Cross-sectional; case-control; prospective	yes	job demands; job control; job strain; ERI	cholesterol; systolic and diastolic blood pressure; ambulatory blood pressure; fibrinogen	Mixed findings for an association between work stress and cardiometabolic risk factors. Risk factors should be included in studies to develop a better understanding of the mechanisms by which job strain leads to disease	M	Schnall et al, 1994
Multiple cardiometabolic factors (cholesterol, blood pressure)	17	Cross-sectional; case-control; prospective	yes	ERI	cholesterol; systolic and diastolic blood pressure	Consistent evidence for an association between work stress and cardiometabolic risk factors.	Y	van Vegchel et al, 2005
blood pressure	20	intervention	yes	job demands; job control; job strain; ERI	systolic and diastolic blood pressure reactivity and recovery	No association between psychosocial work stressors and blood pressure reactivity or recovery	N	Chida & Hammer, 2008
Framingham risk score	single study (N=19 718 men and women)	cross-sectional	n/a	job demands; job control; work social support; job strain; iso-strain	total cholesterol; HDL-cholesterol; systolic blood pressure	No support for the hypothesis that the psychosocial work environment is strongly associated with cardiometabolic risk in healthy workers	N	Pelfrene et al, 2003
metabolic syndrome	single study (N=6452 men and women)	prospective	n/a	chronic iso-strain	metabolic syndrome (ATPIII definition)	Stress at work is an important risk factor for the metabolic syndrome	Y	Chandola et al, 2006

Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.9 Evidence from reviews on the association between cardiometabolic factors and risk of type 2 diabetes

No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
unknown	cross-sectional; prospective	no	blood pressure; blood lipids (triglycerides, LDL, HDL)	incident/prevalent T2DM	Patients with even minimal abnormalities in any 3 of the 5 risk factors for the metabolic syndrome are at heightened risk for diabetes.	Y	Smith, 2007
unknown	cross-sectional; prospective	no	blood pressure; blood lipids (triglycerides, LDL, HDL)	incident/prevalent T2DM	The metabolic syndrome, a clustering of cardiovascular and metabolic risk factors that includes abdominal obesity is strongly associated with the development of diabetes	Y	Haffner, 2006
unknown	cross-sectional; prospective	no	blood pressure; blood lipids (triglycerides, LDL, HDL)	incident/prevalent T2DM	Primary care physicians play a critical role in the early identification and treatment of patients at increased risk for the development of type 2 diabetes	Y	Rader et al, 2007

*Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.10 Evidence from reviews and individual studies on the association between psychosocial work stressors and inflammatory markers

Studies reviewed	Study design	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
9	cross-sectional	no	job demands; job control; work social support; job strain	fibrinogen	Adverse job characteristics may be related to plasma fibrinogen concentrations and this relation is more relevant in female workers	M	Theorell (2002)
12	cross-sectional	yes	job demands; job control; work social support; job strain; ERI	fibrinogen; Vwf; factor VII	Chronic psychosocial work stressors are related to a hypercoagulable state reflected by increased procoagulant molecules	M	von Känel et al, 2001
single study (N=1121 men and women)	prospective	n/a	job demands; job control; work social support; job strain; iso-strain	fibrinogen; CRP; WBC count	the physiological mechanism linking the demand/control/support model with cardiovascular morbidity probably does not include inflammatory processes in the body.	N	Shirom et al, 2008
single study (N=892 men)	Cross-sectional	n/a	job demands; job control; work social support	fibrinogen; CRP; serum amiloid A	Results confirm previous findings regarding elevated plasma fibrinogen and low job control	M	Clays et al, 2005
single study (N=283 men and women)	Cross-sectional	n/a	job demands; job control	CRP; IL-6; serum amiloid A	No evidence for an association between psychosocial work characteristics and inflammatory markers	N	Hemingway et al, 2003
single study (N=3265 men and women)	Cross-sectional	n/a	job demands; job control; job strain	fibrinogen	Job demands and job strain were associated with higher fibrinogen in men. No associations were observed in women.	M	Hirokawa et al, 2008
single study (N=3265 men and women)	intervention	n/a	job control	fibrinogen	Low job control may influence cardiovascular disease risk in men partly through provoking greater fibrinogen stress responses	M	Steptoe et al, 2003
single study (N=10 382 men and women)	Cross-sectional	n/a	job demands; job control; job strain	fibrinogen	The results do not support the hypothesis that job strain has an adverse impact on fibrinogen levels	N	Alfredsson et al, 2002

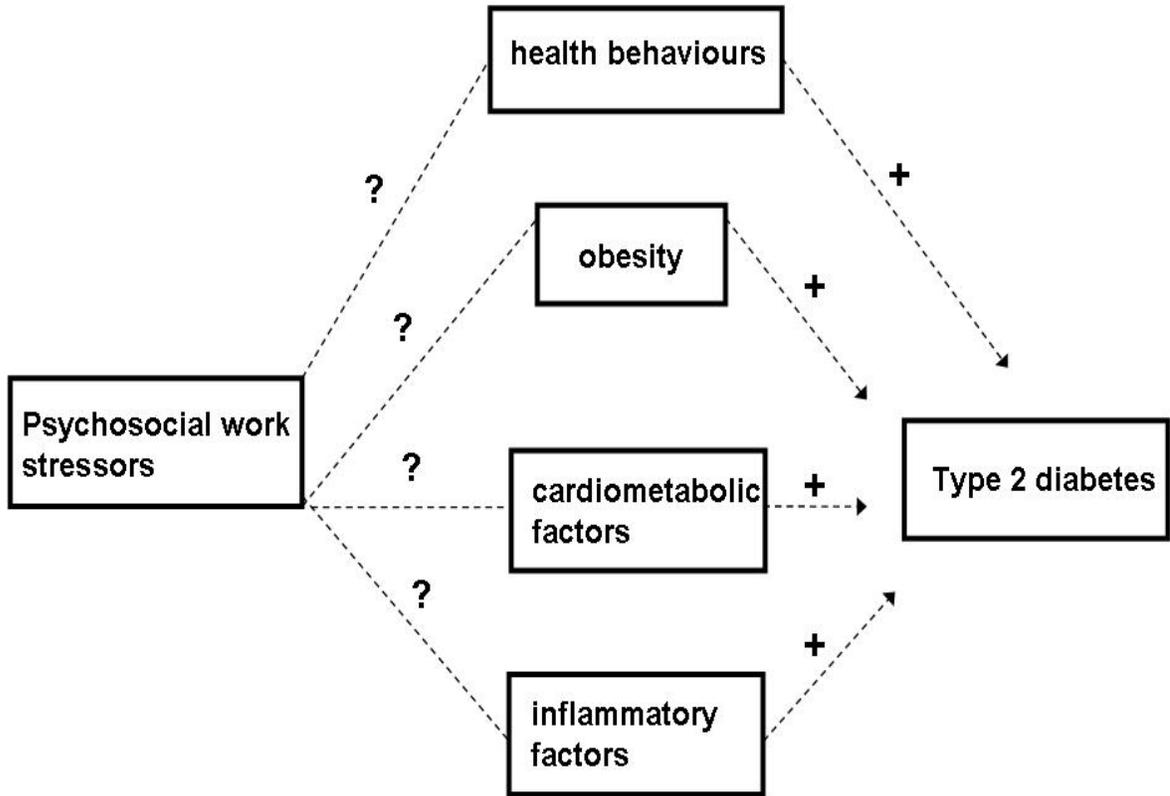
Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Table 2.11 Evidence from reviews on the association between inflammatory markers and risk of type 2 diabetes

No. of studies reviewed	Type of studies	Quantitative assessment of evidence	Exposures assessed	Outcomes assessed	Conclusions	Evidence for association*	Reference study
unknown	cross-sectional; prospective	no	CRP; IL-6; IL1; TNF- α ; sialic acid	incident/prevalent T2DM	These findings suggest that subclinical inflammation may be a contributing factor not only to the aetiology of T2DM but also its cardiovascular complications	Y	Pradhan, 2007
17	prospective	yes	CRP; IL-6; fibrinogen; Vwf; factor VII; TNF- α ; sialic acid	incident T2DM	Intervention studies targeting these pathways would help to determine the contribution of an activated innate immune system to the development of type 2 diabetes	Y	Kolb & Mandrup-Poulsen, 2005
unknown	cross-sectional; prospective	no	CRP; IL-6; IL-1; fibrinogen; Vwf; factor VII; TNF- α	incident/prevalent T2DM	Further research is needed to confirm and clarify the role of innate immunity in type 2 diabetes	Y	Pickup, 2004

*Y=evidence for an association; N=no evidence for an association; M=mixed evidence for an association

Figure 2.2 Evidence on hypothetical pathways linking psychosocial work stressors to type 2 diabetes from the current literature review



2.4 Summary of literature review and gaps in knowledge

The literature review identified the following based on its initial objectives:

- Five studies investigated the effect of psychosocial work stressors (demand/control support and ERI models) on T2DM of which 2 were prospective. For job strain 3 out of 4 studies found an effect and for ERI the single prospective study found an effect. Evidence on this association therefore is limited but relatively consistent.
- There is a consistent finding of gender differences in the association between the demand/control/support model, with 3 of 3 studies that investigated the effect in both genders finding an association among women but not men.
- There is lack of evidence on the association between iso-strain (high demands/low control/low work social support) and risk of T2DM.
- There is no evidence in the literature on the excess risk and population impact associated with exposure to psychosocial work stressors in relation to T2DM.
- There is mixed and inconclusive evidence for an association between psychosocial work stressors and potential mediators (health behaviours, obesity, cardiometabolic and inflammatory). The strongest evidence on these pathways was observed for physical activity, smoking, obesity and fibrinogen levels.
- There is overwhelming evidence for an association between health behaviours, obesity, and cardiometabolic and inflammatory factors and risk of T2DM.

This literature review identified a gap in evidence on the *prospective* effect of psychosocial work stressors on risk of T2DM, as well as for the impact of psychosocial work stressors on T2DM and the pathways linking the two. As in all reviews, there is a possibility that publication bias may operate, with analyses with null or negative associations not been published. The gender differences observed in the reviewed studies need confirmation from other studies and there is also a need for investigation of the association between iso-strain and T2DM risk. There is a need for analyses explicitly aiming at investigating the pathways linking psychosocial work stressors to T2DM. The evidence on the pathways between psychosocial work stressors and T2DM from the current literature review is summarised in figure 2.2.

The current research project aims to address the gaps in research described above. Detailed description of the aims and specific objectives of the current project are presented in the next chapter.

Chapter 3: Aims and objectives

In the previous chapter the gaps in knowledge for the effect and impact of psychosocial work stressors on T2DM and the mechanisms involved were identified. The current research project aims to address these gaps in knowledge. The main aims of the current project as well as specific objectives for each aim are listed below.

3.1 Project aims

1. To investigate the prospective effect of psychosocial work stressors on risk of type 2 diabetes in a population of middle-aged, white-collar men and women in the Whitehall II study (chapters 5-7).
2. To investigate the impact of psychosocial work stressors on risk of type 2 diabetes in a population of middle-aged, white-collar men and women in the Whitehall II study (chapter 8).
3. To elucidate direct and indirect pathways linking psychosocial work stressors to type 2 diabetes among participants of the Whitehall II study (chapter 9).

3.2 Project objectives

Aim 1: To investigate the prospective effect of psychosocial work stressors on risk of type 2 diabetes in a population of middle-aged, white-collar men and women in the Whitehall II study.

Objectives:

1. To examine the incidence of T2DM over 20 years of follow-up in the Whitehall II study (chapter 5).

2. To identify potential confounders or mediators in the association between psychosocial work stressors and T2DM (chapters 6 and 7).
3. To assess the age-adjusted and multivariate adjusted association between components of the 2 main models of psychosocial work stress (demand/control/support and effort-reward-imbalance) and incident T2DM (chapter 7)
4. To investigate effect modifications in the association between psychosocial work stressors and incident T2DM by gender, age, employment grade and obesity (chapter 7).

Aim 2: To investigate the impact of psychosocial work stressors on risk of type 2 diabetes in a population of middle-aged, white-collar men and women in the Whitehall II study.

Objectives:

1. To estimate the attributable risk and fraction (excess risk) and population attributable risk and fraction (population impact) for psychosocial work stressors on incident T2DM (chapter 8).
2. To compare the population impact of psychosocial work stressors with that of traditional behavioural and biological risk factors.
3. To estimate the combined attributable risk on incident T2DM of psychosocial work stressors and traditional behavioural and biological risk factors and calculate the additional excess risk due to work stressors (chapter 8).

Aim 3: To elucidate direct and indirect pathways linking psychosocial work stressors to type 2 diabetes among participants of the Whitehall II study

Objectives:

1. To assess unadjusted and adjusted cross-sectional (phase 3) associations between psychosocial work stressors and behavioural and biological factors associated with incident T2DM among men and women in the Whitehall II study (chapter 9).
2. To assess the mediating effects of behavioural and biological risk factors, individually and in combination, on the work stressors-incident T2DM association (chapter 9).

Chapter 4: Methods

4.1 Study setting and population

4.1.1 The Whitehall II study

4.1.1.1 Reason for setting up the study and general aim

The Whitehall II study was set up in 1985 as a new longitudinal study of British civil servants, with the explicit intention of examining the reasons for the social gradient in health and disease among men and women (Marmot and Brunner, 2005). The first Whitehall study was set up in 1967 and recruited 18 403 middle-aged male civil servants in London. While the investigation of social determinants of health and disease was not among the initial aims of the first Whitehall study, analysis of cardiovascular disease by employment grade revealed a stepwise increase in cardiovascular mortality and morbidity the lower the socioeconomic position (Marmot et al, 1978). When conventional risk factors (blood pressure, blood cholesterol and smoking) were controlled for, two-thirds of the cardiovascular mortality risk differential between the lowest and highest civil service employment grades remained unexplained (Rose & Marmot, 1981).

The Whitehall II study specifically aimed to investigate the factors contributing to the social inequality in morbidity and mortality beyond the established risk factors (blood pressure, cholesterol, smoking, high alcohol consumption, physical inactivity), with a specific emphasis on psychosocial work stressors. The specific aims of the study were the following (Marmot & Brunner, 2005):

1. Investigate the effect on health and disease of the work environment (psychological workload, control over work pacing and content, opportunity for use of skills, social support at work).
2. Investigate the moderating effect on these relationships of social supports

3. Investigate the interaction between these psychosocial factors and other established risk factors in the aetiology of chronic disease

4.1.1.2 Funding, ethics and consent

The Whitehall II study has been funded by the Medical Research Council (MRC), British Heart Foundation (BHF), the National Heart Lung and Blood Institute (NHLBI; USA) and the National Institute on Ageing (NIA; USA). Ethical approval for the study was obtained from the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee Alpha). All participants gave written informed consent for their participation in the study.

4.1.1.3 Baseline sampling and recruitment

The target population for the Whitehall II study was all civil servants aged 35–55 years working in the London offices of 20 Whitehall departments in 1985–88. The response rate, after excluding those who were ineligible, was 73% (74% among men; 71% among women). The response rate varied by employment grade (81% among the high employment grade categories; 68% among the lower grades). The true response rate is likely to be higher because around 4% of those on the list of employees had in fact moved before the study and were thus not eligible for inclusion. The achieved sample size was 10 308 civil servants, 3413 women and 6895 men.

4.1.1.4 Baseline data collection

At study baseline (1985-88), a self-administered questionnaire was posted to participants. The questionnaire was checked for completeness at the screening examination by an interviewer who sought missing responses and was later checked for validity. The questionnaire included the following: (1) social and demographic data; (2) health status measures; (3) psychosocial work characteristics; (4) social networks and type of social supports; (5) health behaviours (smoking, diet, alcohol consumption, physical activity); and (6) psychosocial factors outside work and psychological traits (including the

Framingham type A score, Cook-Medley hostility, stressful life events and personal difficulties).

Participants attended for a screening examination at their place of work. The screening included measurement of height, weight, blood pressure, as well as collection of blood samples for assessment of blood cholesterol, apolipoproteins and inflammatory markers. Collection and storage of blood samples was conducted in the following way:

Venepuncture of the left antecubital vein was performed with tourniquet. Blood was collected into plain, citrate or Sarstedt monovettes. After centrifugation samples were immediately frozen at -80 °C and stored until assay. Serum for lipid analysis was refrigerated at -4 °C and assayed within 72 hours. Plasma was prepared by collection of blood into polypropylene tubes containing sodium citrate to produce a final concentration of 0.38% sodium citrate, which was immediately centrifuged and frozen at -70°C (Marmot et al, 1991, Brunner et al, 1993).

4.1.1.5 Follow-up phases

After the initial clinical examination (1985-1988), further waves of data collection were carried out including questionnaire phases (i.e. only questionnaire administered to participants) and clinical phases (both questionnaire and clinical examination). Table 4.1 provides a timeline for the phases of data collection of the WII study, including those planned up to 2011.

Table 4.1 Data collection phases of the Whitehall II study from baseline (1985-88) up to 2011

Phase	Dates	Type	Number of participants
1	1985-1988	Screening / questionnaire	10 308
2	1989-1990	Questionnaire	8132
3	1991-1994	Screening / questionnaire	8815
4	1995-1996	Questionnaire	8628
5	1997-1999	Screening / questionnaire	7870
6	2001	Questionnaire	7355
7	2002-2004	Screening / questionnaire	6968
8	2006	Questionnaire	7180
9	2007-2009	Screening / questionnaire	Underway ~ 6500
10	2011	Questionnaire	Planned

At phase 3 (1991-93) the questionnaire was supplemented by a detailed dietary assessment including both a food-frequency questionnaire and a diet diary (Stallone et al, 1997; Brunner et al, 2001). In the clinic, a 75g oral glucose tolerance test (OGTT; fasting and 2 hour glucose and insulin) was administered to participants for ascertainment of diabetes (Brunner et al, 1997). Diabetes ascertainment is described in sub-section 4.2.2.1. Additional screenings were carried out for the following: fasting and post-load (2-hour) insulin; waist and hip circumference; and more detailed assessment of blood lipids and inflammatory/coagulation markers.

The participation rate at phases 3, 5 and 7 (clinical examination phases used in the current project) was 83%, 76% and 65% respectively. The number of participants in the clinical examination was 7904 at Phase 3, 6554 at phase 5 and 6483 at Phase 7.

4.1.1.6 Reliability of screening examination

At phase 3, short-term biological variation and laboratory error were estimated by assaying blinded duplicate samples for 5% of participants. A sub-sample of 323 participants returned after 2-4 weeks in order to estimate reliability (between-person variability as a proportion of total variability). Average elapse time between samples was 22 (SD 10.5) days. Reliability between samples was assessed with Pearson's correlation

coefficients. Intra-class correlations, for selected measures were: ≥ 0.93 for anthropometric measures (except for hip circumference in women, 0.86); 0.58 and 0.52 for fasting glucose and insulin respectively and 0.66 and 0.58 respectively for the 2h samples; 0.78-0.97 for lipid measurements; 0.66 for fibrinogen, 0.77 for CRP, 0.61 for IL-6 and 0.75 for vWF. Multilevel modeling (MLn) showed that diurnal variation was a source of variance in the glucose tolerance test results. For 2-h values of glucose and insulin respectively 8.7% and 6.0% of between-subject variation, and 10.3% and 4.9% of within-subject variation was attributable to time of sample.

4.1.1.7 Whitehall II psychobiology sub-study

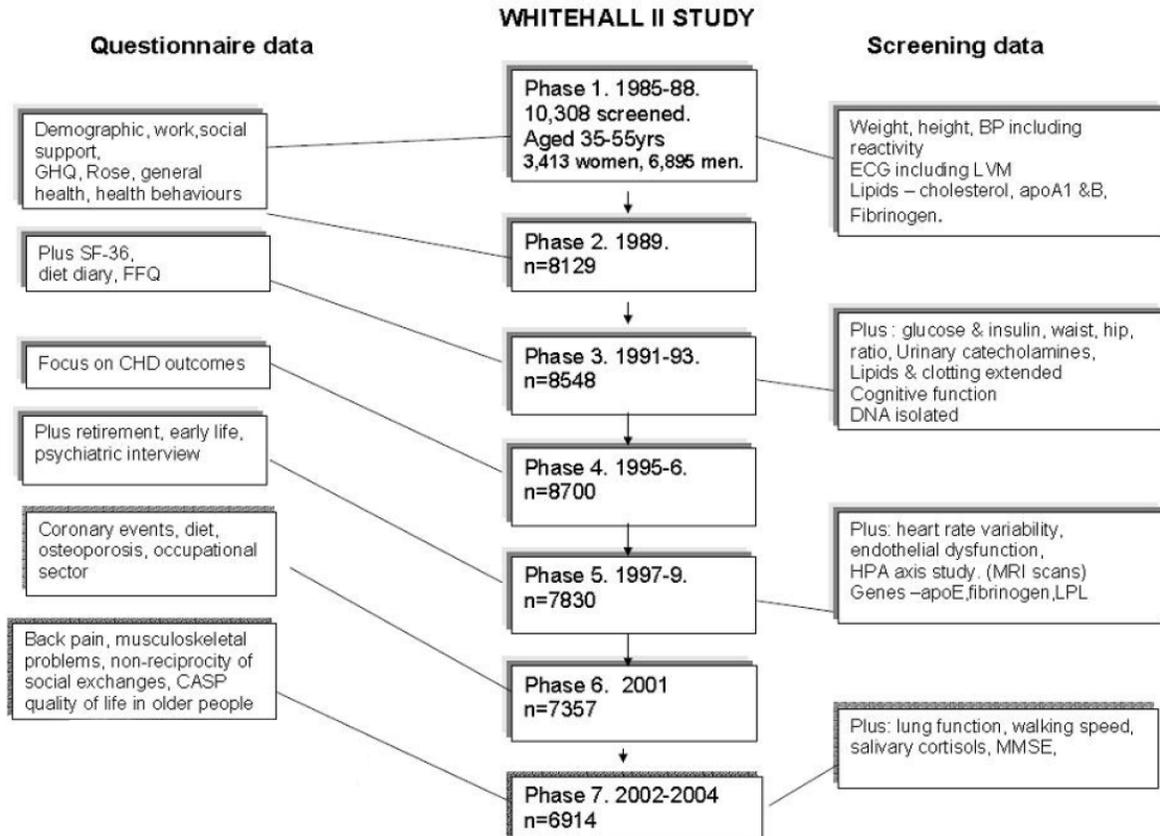
At phase 5, a further sub-study of 228 participants (123 men, 105 women) was set up, with the name “Whitehall II psychobiology sub-study”. Participants of that sub-study underwent psychophysiological stress testing in 1999 to 2000 (Steptoe et al, 2002). Participants were of white European origin, aged 45 to 59 years, lived in the London area, in full-time work, and had no history or objective signs of CHD and no previous diagnosis or treatment for hypertension. Selection was stratified by grade of employment (as a marker of SEP) to include higher and lower status participants. The current project does not use any data from the Whitehall II psychobiology sub-study, but evidence generated from the sub-study will be discussed due to its relevance in strengthening the case for a causal association between psychosocial work stressors and T2DM.

4.1.1.8 Whitehall II phases used in the current project

This project uses data from the WII study phase 1 (1985-88) to phase 7 (2002-04). Phase 3 (1991-93) was the baseline used in the main analysis. As described in sub-section 4.1.1.5, phase 3 was the first phase that clinical ascertainment of T2DM with an OGTT TOOK PLACE. Identifying prevalent cases accurately at baseline is critical in survival analysis, as inclusion of prevalent baseline cases has the potential to bias the results. The issue of bias in the analysis is described in a subsequent section. The main exposure variables (psychosocial work stressors) were also derived from phase 3. Other analyses from the WII study assess phase 1-3 work stressors in relation to disease incidence

(Chandola et al, 2006; Brunner et al, 2007; Chandola et al, 2008). This approach was not followed for the current project in order to avoid long relapse time between exposure assessment and disease ascertainment. As the focus of the project is incidence of T2DM, data on diabetes status was used from all phases up to phase 7. No data on diabetes after phase 7 was used as these data were not available for analysis at the beginning of the project in 2006. The main confounding and mediating variables were obtained from phases 1-3. Phase 1 and/or 2 variables were used in the case that the specific variables(s) were not measured at phase 3. Due to the nature of the main analysis (survival analysis), the main exposure variables, as well as confounding and mediating variables could not be assessed after the beginning of follow-up (phase 3) as this would introduce bias in the results. Detailed description of variable assessment is given in a subsequent sub-section of the current chapter. Figure 4.1 shows the WII phases used in the current project (study baseline in 1985-88 up to phase 7 in 2002-04).

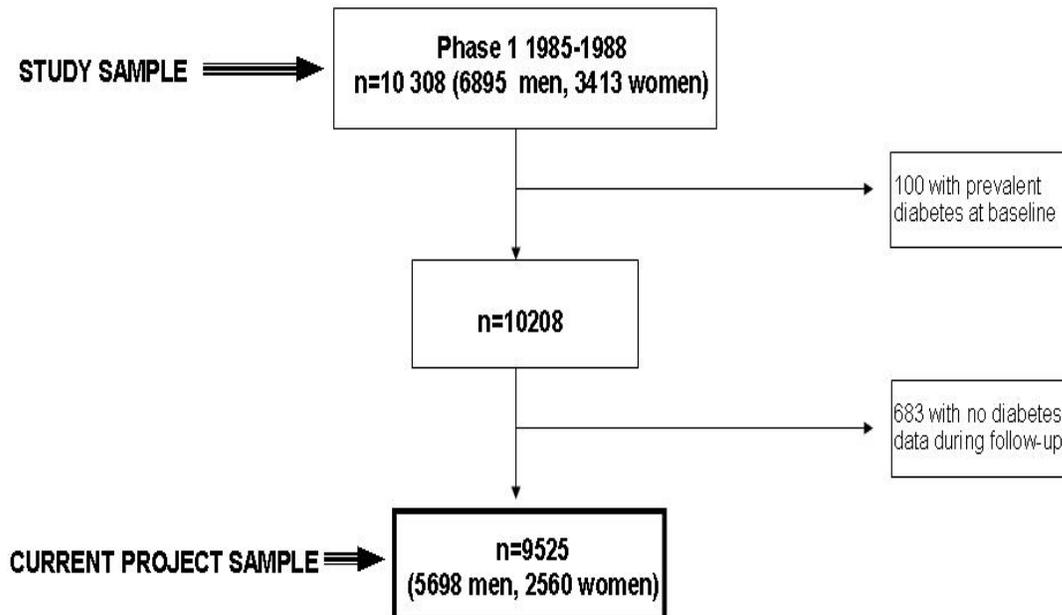
Figure 4.1 Phases of the Whitehall II study from study baseline (1985-88) up to phase 7 (2002-04)



4.1.2 Project population and sample

The population under study is all civil servants aged 35-55, who were free from T2DM at study baseline in 1985. Of the sample of 10 308 participants, 100 reported having diabetes at phase 1. Those who contributed no information about diabetes status at all phases (N=683) were omitted from the analysis. The eligible sample contained 9525 participants (5698 men and 2560 women).

Figure 4.2 Whitehall II study sample and the sample selected for analysis in the current project



4.2 Variables

4.2.1 Variable selection

In the WII study some variables used in this project were already derived for previous analyses, so there was not need to derive them again. These are referred to as ‘ready’ variables in this methods chapter. Some variables needed for the current project were not available and had to be derived. These are referred to as ‘derived’ variables in the methods chapter. Psychosocial work stressor variables, even though ready from previous analyses, they were derived again from the component measures in the current project. Appendix 2 gives a brief description of all the variables used, also stating whether they were obtained ready for analysis or were specifically derived for the current project.

4.2.1.1 Selection of potential confounders and mediators

4.2.1.1.1 Potential confounding variables

The variables potentially confounding the psychosocial work stressor-incident T2DM association were chosen *a priori*. Selection of these variables was based on theory presented in the introduction and literature review (chapters 1 and 2). Potential confounding factors were chosen on the basis that: (1) there was evidence for an association between these variables and T2DM in the literature AND; (2) there was evidence (or suggestion) in the literature for an association between psychosocial work stressors and these variables; AND (3) these variables were *not* in the causal pathway between psychosocial work stressors and incident T2DM. The chosen variables were categorised as: (i) socioeconomic factors; (ii) psychosocial factors outside work; (iii) psychological traits; and (iv) reproductive factors in women.

Three SEP indicators were used spanning from early life to adulthood. The SEP indicators chosen were: (i) father's social class; (ii) educational attainment; and (iii) civil service employment grade. The psychosocial factors outside work and the psychological traits chosen for analysis were the ones assessed at the WII study baseline: (i) life satisfaction; (ii) life events; (iii) isolation; (iv) anger; (v) hostility; (vi) affect balance; (vii) type A personality; and (viii) general psychological wellbeing. The reproductive factors assessed in WII study were: (i) menopausal status; (ii) hormone replacement therapy; and (iii) use of oral contraceptive medication.

4.2.1.1.2 Potential mediating variables

Potential mediating factors were also chosen *a priori* on the basis that: (1) there was evidence for an association between these variables and T2DM in the literature AND; (2) there was evidence (or suggestion) in the literature for an association between psychosocial work stressors and these variables; AND (3) these variables *are* in the causal pathway between psychosocial work stress and incident T2DM. The selected variables were grouped into: (i) behavioural factors; and (ii) biological factors. Within the biological factors the following sub-groups of factors were decided as potential mediators: (i) anthropometric factors; (ii) cardiometabolic factors; and (iii) inflammatory factors.

For health behaviours the following variables were used based on theory and evidence presented in the introduction and literature review chapters: (i) alcohol consumption; (ii) smoking status; (iii) physical activity; and (iv) three different diet measures. The diet variables included a variable used previously in the WII study, namely diet patterns and 2 derived variables. The derived variables were wholegrain cereal consumption and dietary energy density. Biological factors were also chosen based on theory and evidence supporting a potential mediating effect in the work stressor-incident T2DM association (chapters 1 and 2). These were: (i) BMI (ii) waist circumference; (iii) waist-hip ratio (WHR); (iv) waist-height ratio (WHtR) (derived variable); (v) systolic blood pressure; (vi) triglycerides; (vii) HDL-cholesterol; (viii) fibrinogen; (ix) CRP; (x) IL-6; (xi) von Willebrand factor (vWf); and (xii) factor VII. Several inflammatory markers have been linked to increased risk of T2DM but in the WII study the assessed inflammatory markers were limited to the ones mentioned above.

Appendix 3 shows how each of these categories of factors could confound or mediate the work stress-incident T2DM association.

4.2.2 Variable assessment and development

4.2.2.1 Type 2 diabetes

At phases 1 and 2, no clinical screening for diabetes took place and type 2 diabetes was ascertained from the question: “Do you suffer from diabetes”, as well as a question on use of diabetic medication. At the phase 3 clinical examination the first oral glucose tolerance test for type 2 diabetes was administered. Participants were asked “Has a physician ever told you that you have diabetes?” If the participant answered yes, they were not asked to fast and did not undergo the OGTT. The OGTT was administered following an overnight fast or in the afternoon after no more than a light fat-free breakfast eaten before 8am. After the initial venous blood sample, participants drank 389 ml ‘Lucozade’ (equivalent to 75 g anhydrous glucose) over 5 minutes. A second blood sample was taken 2 hours later. Subsequent clinical assessments for type 2 diabetes took

place at phases 5 and 7. Blood glucose was determined in fluoride plasma by an electrochemical glucose oxidase method. Technical error was estimated by assaying blinded duplicate samples for 5% of participants. Coefficients of variation for glucose were 2.0-6.6% (Brunner et al, 1997). For 2h glucose, 8.7% of between-subject variation, and 10.3% of within-subject variation was attributable to time of sample. This effect was controlled for by adjusting fasting and post-load glucose and insulin to a sample time of 12.00 hours (Brunner et al, 1997).

Diabetes was ascertained according to the World Health Organisation definition. Definition is based on valid glucose values only (i.e. non-fasting glucose values have been excluded). For participants with only a fasting glucose value, the classification was derived based on that value only. For participants with a full 2-hour glucose tolerance test (OGTT) both fasting and 2-hour values were used for classification. Ascertainment of incident T2DM was supplemented by self-reported doctor-diagnosed diabetes and use of diabetic medication at phases 2-7 with the following question: “Has a physician ever told you that you have diabetes?” The current UK definition of diabetes used was a 2-hour glucose tolerance test finding of ≥ 11.1 mmol/L (200 mg/dL) or a fasting glucose level of ≥ 7.0 mmol/L (≥ 126 mg/dL) (World Health Organization, 1999) or physician-diagnosed diabetes and/or use of diabetic medication.

4.2.2.2 Psychosocial work stressors

4.2.2.2.1 Demand/control/support model (job strain and iso-strain)

In the Whitehall II study, job demands, decision latitude (job control) and work social support were measured using self completion questions derived from the Job Strain Questionnaire (Karasek & Theorell, 1990). Decision latitude can be subdivided into two components: decision authority, the amount of control over work; and skill discretion, a measure of job variety and opportunity for use of skills at work. Work social support has three components: support from colleagues; support from supervisors; and clarity and consistency of information from supervisors. The three mentioned scales were derived by adding the scores of each question item belonging to each scale (tables 4.2 and 4.3).

According to Karasek and Theorell (1990), high job demands was defined as above the median score on the job demands scale. Low job control was defined as below the median score on the job control scale. The work social support scale was divided into tertiles and the lowest tertile was defined as low work social support according to the first publication on the iso-strain model (Johnson and Hall, 1988). Job strain was present when the participant simultaneously scored high on the job demands questions and low on the decision latitude (job control) questions (Kuper et al, 2003). Participants in the lowest tertile of work social support who were also identified with job strain were defined as having iso-strain (Chandola et al, 2006).

Table 4.2 lists the question items used to assess the job strain and iso-strain models of psychosocial work stress. Figure 4.3 displays the concepts of the demand/control/support model.

Table 4.2 Question items of the demand/control/support model of psychosocial work stress

Job demands

- Do you have to work very fast?
- Do you have to work very intensively?
- Do you have enough time to do everything?
- Do different groups at work demand things from you that you think are hard to combine?

Decision latitude (Job control)

Decision authority

- Do you have a choice in deciding HOW you do your work?
- Do you have a choice in deciding WHAT you do at work?
- Others take decisions concerning my work.
- I have a good deal of say in decisions about work.
- I have a say in my own work speed.
- My working time can be flexible.
- I can decide when to take a break.
- I have a say in choosing with whom I work.
- I have a great deal of say in planning my work environment.

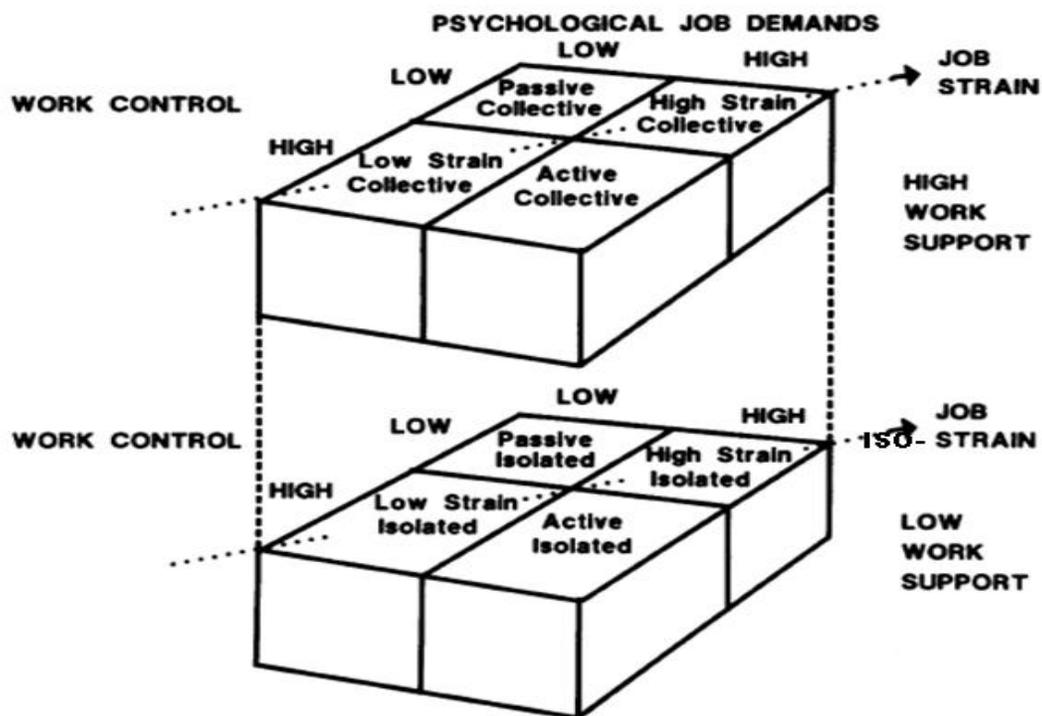
Skill discretion

- Do you have the possibility of learning new things through your work?
- Does your work demand a high level of skill or expertise?
- Does your job require you to take the initiative?
- Do you have to do the same thing over and over again?
- Does your job provide you with a variety of interesting things?
- Is your job boring?

Social support at work

- Do you get sufficient information from line management (your superiors)?
- Do you get consistent information from line management (your superiors)?
- How often do you get help and support from your colleagues?
- How often are your colleagues willing to listen to your work-related problems?
- How often do you get help and support from your immediate superior?
- How often is your immediate superior willing to listen to your problems?

Figure 4.3 The demand/control/support model of psychosocial work stress



4.2.2.2.2 The Effort-Reward Imbalance model

At phase 3, the ERI scale was derived using the phase 5 data as the starting point. Exploratory factor analysis was performed on phase 3 work characteristic measures to identify items from the phase 3 questionnaire that loaded onto factors similar to extrinsic effort and reward measured at phase 5. Numerous iterations led to factors that were tested against the Siegrist items at phase 5 (extrinsic effort and reward separately) using confirmatory factor analysis (Kuper et al, 2002). This analysis was used for choosing the items for the extrinsic efforts at work scale and the rewards at work scale. The scales were constructed by adding the scores of the corresponding items for each scale. Table 4.3 lists the 15 questions of the extrinsic effort and reward scales. Effort-Reward-Imbalance was derived as: $\text{Extrinsic effort scale} \times 2 / \text{Reward scale}$ (Kuper et al, 2002).

Components of the ERI model were also dichotomized as high efforts at work (highest tertile of efforts scale) and low rewards at work (lowest tertile of rewards scale). ERI was also assessed as a categorical variable with the following 3 categories: (i) low efforts AND high rewards; (ii) either high efforts OR low rewards; and (iii) high efforts AND low rewards. Figure 4.4 displays the concepts of the ERI model.

Table 4.3 Question items of the effort-reward imbalance model of psychosocial work stress

Extrinsic efforts at work

Do you have to work fast?

Do you have to work intensively?

Do you have enough time for everything?

Does your work demand a high level of skill and expertise?

Does your work require you to take the initiative?

Rewards at work

Does your work provide a variety?

Is your work boring?

Do you consider your work very important?

Do your bosses consider your work important?

Do your colleagues consider your work important?

Do you wish you had another job?

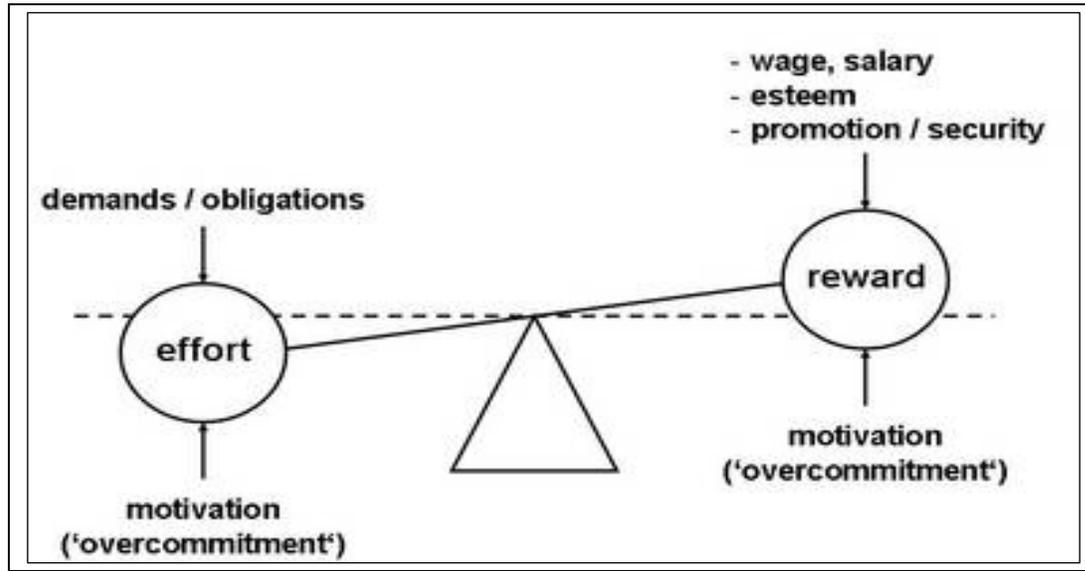
Are you working just for the money?

Does your job contribute to society?

How often do you get help and support from your colleagues?

How often do you get help and support from your boss?

Figure 4.4 The effort-reward-imbalance model of psychosocial work stress



4.2.2.2.3 Validity and reliability of psychosocial work stressor measures

4.2.2.2.3.1 demand/control/support model

In the WII study, the components of the demand/control/support model of psychosocial work stress were derived from the main questions of the original Job Strain Questionnaire (Karasek & Theorell, 1990). Principal components analysis was used to derive the following three scales: (i) job demands (4 items; Cronbach's $\alpha = 0.67$): (ii) decision latitude (15 items; Cronbach's $\alpha = 0.84$) and (ii) work social support (6 items; Cronbach's $\alpha = 0.79$) (Stansfeld et al, 1998)

In the WII study in 18 out of 20 departments 140 personnel managers assessed each job, independently of the holder of the post, for the level of job demands and control. This external assessment could be considered a more objective measure of the work environment in that it was made independently of the participants' perceptions of the job. There was moderate agreement between the objective and external assessments (weighted kappa 0.49 -0.51) (Stansfeld et al, 1998).

The empirical association between components of the Job Strain Questionnaire and psychological strain has been previously demonstrated in relation to depression, sleeping problems and exhaustion (Karasek et al, 1981). Job strain as assessed in the current analysis was previously associated with several disease outcomes in the WII study including elements of cognitive decline (Elovainio et al, 2009), minor psychiatric disorder (Stansfeld et al, 1995), heart disease (Bosma et al, 1998; Kuper et al, 2003), obesity (Kivimaki et al, 2006; Brunner et al, 2007) and the metabolic syndrome (Chandola et al, 2006). The definition of iso-strain used in the current analysis has been previously found to predict obesity (Brunner et al, 2007), heart disease (Chandola et al, 2008), and the metabolic syndrome (Chandola et al, 2006).

4.2.2.2.3.2 ERI model

The Effort-Reward imbalance scale in its original form was not available before phase 5. Internal consistency of both reward and extrinsic effort at each iterative stage was checked in order to ensure unidimensionality of the constructs. Principal component analysis was used to derive the scales of extrinsic efforts (5 items; Cronbach's $\alpha = 0.72$) and rewards (10 items; Cronbach's $\alpha = 0.75$).

The empirical association between ERI and psychological strain has been previously demonstrated in relation to emotional 'burnout' (Siegrist, 1998), as well as several psychosomatic symptoms (van Vegchel et al, 2005). The definition of ERI used in this project has been linked to several disease outcomes, including heart disease and related risk factors (increased blood pressure and cholesterol) (van Vegchel et al, 2005; Siegrist, 1996).

In analysis comparing the demand/control/support model (job strain and iso-strain) of and the effort-reward imbalance model with a model of observed work stress (hindrance/utilization) in the WII study, the demand/control/support model explained the most variance in depression and anxiety symptoms (Griffin et al, 2007).

4.2.2.3 Sociodemographic variables

4.2.2.3.1 Age (phases 1 and 3)

Age was treated as a potential confounder in the analysis. Participants reported their date of birth and their age was calculated according to the date of questionnaire completion for each phase of the study. A variable for age group in years was constructed as: 35-39; 40-44; 45-49; and 50-55.

4.2.2.3.2 Employment grade (phases 1 and 3)

The civil service classifies job descriptions by grade title. There are more than 2,000 non-industrial grades which are classified into 12 grade levels. Employment grade is an accurate indicator of education, income and working conditions, hence socioeconomic position. Employment grade was treated as a potential confounder. Participants reported their Civil Service grade title and on the basis of this they were classified according to one of the 12 grade levels. These grade levels reflect differences in salary, level of job responsibility and education. There are 12 non-industrial grades levels (1-14). Levels 4 and 5 do not exist and level 14 comes between 3 and 6 (table 4.4).

Table 4.4 Examples of employment grade titles and levels in the British civil service

Grade title	Grade level
Permanent Secretary	1
Deputy Secretary	2
Under Secretary	3
(Unified Grade 4)	14
Assistant Secretary	6
Senior Principal	7
Principal	8
Senior Executive Officer	9
Higher Executive Officer	10
Executive Officer	11
Administrative Officer	12
Administrative Assistant/ Office Support	13

Participants were assigned to 1 of 6 grades based on salary scale. Grade 1 consists of participants in Unified Grades 1-6 (annual salary range at 1 August 1992, £ 28 904-87 620), grade 2 is equivalent to Unified Grade 7 (£ 25 330-36 019), grade 3 is Senior Executive Officer (£ 18 082-25 554), grade 4 is Higher Executive Officer (£ 14 456-20 850), grade 5 Executive Officer (£ 8517-16,668) and grade 6 Clerical and Office Support staff (£ 6483-11 917). The variable was regrouped in the following 3 categories: (i) High (administrators, the top seven unified grades); (ii) Middle (executives, professionals and technical staff); and (iii) Low (clerical and office support staff).

4.2.2.3.3 Educational attainment (phase 5)

Educational attainment measured as the highest level of education achieved was used as an indicator of SEP in early adulthood. Educational attainment was treated as a potential confounder. In the phase 5 questionnaire the participants answered the following question: “What is the highest level of examination or qualification that you obtained when you first left full-time education?” and chose one of 11 education categories: (i) No academic qualifications; (ii) School Certificate; (iii) Matriculation; (iv) 'O' Level; (v) 'A' Level, SCE Higher; (vi) 'S' Level; (vii) BA/BSC; (viii) University or CNAA Higher degree (e.g. MA/MSc, PhD); (ix) City and Guilds; (x) National Diplomas and Certificates (e.g. ONC, HND, etc.); (xi) Other. These were regrouped into five hierarchical categories: (i) no formal education; (ii) lower secondary education; (iii) higher secondary education; (iv) University degree; (v) higher University degree. For the current analysis a variable with 3 categories was created: (i) no formal education; (ii) secondary education; and (iii) university degree. As educational attainment was assessed at WII phase 5, there is missing information for participants who dropped out between phases 3 and 5. This issue will be discussed in a following sub-section (4.3.2.6.2).

4.2.2.3.4 Father's social class (phase 1)

Father's social class was used as a measure of childhood SEP. Father's social class was treated as a potential confounder. Father's social class was coded to the Registrar

General's Social Classification (RGSC) from the following set of questions in the phase 1 questionnaire: (i) What is/was your father's main job, what kind of work does/did he do in it?; (ii) What qualifications or training if any are/were necessary for that job?; (iii) Is/was he an employee or self employed?; (iv) How many people work/worked at his place of work?; (v) Is/was he in charge of other people?. In the RGSC classification, individuals are assigned to the classes first by being allocated to an occupational group according to the kind of work they do, then each occupational group is assigned as a whole to a social class. The 6 classes are the following: I (Professional, e.g. doctor); II (Managerial and technical' e.g. general manager); IIIN (Skilled non-manual, e.g. sales-assistant); IIIM (Skilled manual, e.g. plumber); IV (Partly-skilled, e.g. agricultural worker); and V (Unskilled, e.g. porter).

4.2.2.4 Psychosocial factors outside work and psychological traits

4.2.2.4.1 Life satisfaction (phase 1)

Life satisfaction was treated as a potential confounder. The life satisfaction variable was assessed using four life satisfaction measures: (i) feeling of financial security, (ii) satisfaction with standard of living, (iii) material deprivation and (iv) general life satisfaction (Singh-Manoux et al, 2003).

4.2.2.4.2 Life events (phases 1)

Life events were treated as a potential confounder. At study baseline, participants were asked to report how much they were upset from a list of stressful life events derived from the original validated 'Life Event and Difficulty Schedule' (Brown & Harris, 1978). Life events included serious personal illness, death of a close relative or friend, illness of a close relative or friend, major financial difficulty, divorce, separation or break of a personal intimate relationship, other marital or family problem, and experience of a mugging, robbery, accident, or similar event. These questions loaded on to a single component in a principal components analysis of eight questions from the original scale, which represented the extent by which participants were upset by life events outside the

workplace during the recent past (scored from 0-21). This measure was previously linked to depression in the WII study (Stansfeld et al, 1998).

4.2.2.4.3 Isolation (phase 1)

Social isolation was treated as a potential confounder. Social networks and support were measured using questions derived by Berkman and Syme (1979). The isolation scale was constructed measuring social networks within the household and beyond, which includes frequency of contact and number of contacts with friends and relatives and participation in social groups.

4.2.2.4.4 Anger (phase 1)

Anger was treated as a potential confounder. Anger was assessed from 10 question-items on personality traits. Participants replied to questions on how easily they get upset and/or angry and at what extent (Spielberger, 1988). From these items an anger score ranging from 0-30 was derived, with higher score denoting greater anger.

4.2.2.4.5 Hostility (phase 1)

Hostility was treated as a potential confounder. Hostility was assessed using an abridged 38-item version (Cronbach's $\alpha=0.83$) of the original 50-item Cook-Medley Hostility Scale (Cook and Medley, 1954) in phase 1. The internal consistency, test-retest reliability, and construct validity of this scale have been demonstrated in a review by Smith (1992). The hostility variable derived was scored from 0 to 37, with higher scores denoting greater hostility.

4.2.2.4.6 Affect balance (phase 1)

Affect balance was treated as a potential confounder. The 10-item Bradburn affect balance scale was used to assess how participants felt during the past weeks. Participants replied to questions on frequency and intensity of several positive and negative feelings. The positive and negative affect scales were scored from 0-15. Affect balance was

calculated as positive affect minus negative affect and scored from -15 to +15 (Nabi et al, 2008).

4.2.2.4.7 Type A personality (phase 1)

Type A personality was treated as a potential confounder. Type A personality was assessed by the 10-item Framingham Type A questionnaire. Participants replied to questions about competitiveness, negative feelings, time pressure and need for domination. The derived type A personality scale was scored from 0 to 30 (Haynes, 1978).

4.2.2.4.8 General psychological wellbeing (phases 1-3)

The General Health Questionnaire (GHQ) score was treated as a potential confounder. General psychological wellbeing was assessed by a 30-item version of the General Health Questionnaire measuring non-psychotic psychological distress at phases 1, 2 and 3. The GHQ is a well-established screening questionnaire for non-psychotic psychological distress, largely depression and is suitable for use in general population studies. All the GHQ items were scored on a Likert scale from 0 to 3. The phase 1 questionnaire was validated against a clinical interview in a sub-sample of the participants (Stansfeld and Marmot, 1992). Chronic GHQ score was calculated using information from the phase 1, 2 and 3 questionnaire and ranges from 0 to 30, with higher score denoting higher morbidity (Stansfeld et al, 1999).

4.2.2.5 Behavioural variables

4.2.2.5.1 Diet measures (phase 3)

Diet measures were treated as potential mediators in the work stressors-incident T2DM association. Participants attending the phase 3 clinic were asked to take home and complete a 127-item semi-quantitative food frequency questionnaire (FFQ) (Willett et al, 1985). A total of 5430 participants (83% of those who participated at the phase 3 clinic)

completed the questionnaire (Brunner et al, 2001). A common unit or portion size for each food (e.g. one slice of bread) was specified, and participants were asked how often, on average, they had consumed that amount of the item during the previous year. The nine responses ranged from 'never or less than once per month' to 'six or more times per day'. Frequency of intake per day was calculated by dividing the per week consumption by 7. Intake in grams per day was computed for all food items by multiplying the per day frequency of consumption by the weight of a standard portion of the specified food. For example, for a participant who reported consuming white bread 7 times a week, the intake of white bread in grams per day was calculated as follows:

$$\text{Per day intake} = 7/7 = 1$$

$$\text{Average portion of white bread (g)} = 30$$

$$\text{Grams per day} = 30 \times 1 = 30 \text{ g}$$

Energy (kcal) content of the reported food items was calculated using the nutrient composition of foods obtained from the 4th and 5th editions of The Composition of Foods and supplementary tables.

4.2.2.5.1.1 Food frequency questionnaire validation

Phase 3 included data assessment by both a FFQ and a 7-day diet diary (7DD) and biomarkers of nutrient intake (Brunner et al, 2001). The validation sample was composed of an age- and employment grade-stratified random sub-sample of the main cohort (457 men and 403 women), aged 39–61 years, who completed both a 7DD and a FFQ at phase 3. Serum cholesteryl ester fatty acids, plasma a-tocopherol and b-carotene were measured as biomarkers. Estimates of mean energy intake from the FFQ and 7DD were similar in men, and ~10% higher according to the FFQ in women. Quartile agreement for energy-adjusted nutrient intakes comparing the FFQ with the 7DD was in the range 37–50% for men and 32–44% for women and for alcohol 57% in both sexes. Some examples of agreement between FFQ nutrient intake and biomarkers are: energy-adjusted carotene intake vs. b-carotene/cholesterol (Spearman rank correlations (ρ), men=0.32, women=0.27); energy-adjusted % fat intake vs. serum cholesteryl ester fatty acids (ρ

men=0.38, women= 0.53). For a-tocopherol there were no correlations between plasma level and estimated intakes by the FFQ. The validation study showed that against the available biomarkers, the machine-readable FFQ performed as well as the manually coded 7DD. Intake of specific key nutrients was well estimated by the FFQ against plasma biomarkers, apart from vitamin E intake probably reflecting misreporting in consumption of vegetable oils.

4.2.2.5.1.2 Dietary energy density

Dietary energy density is a holistic measure of diet quality and was specifically derived for the current project. Dietary energy density was calculated as average calories consumed per gram of food. In order to calculate dietary energy density, energy consumed from solid foods (i.e. not from beverages) and the weight of diet per day were calculated for each participant (Cox & Mela, 2000).

Total diet weight from food was calculated by adding the average per day weight of all the food items that each participant reported eating during the last month. For example:

Diet weight (grams/day) = beef + chicken + white bread + cheese + apples + +etc.

Energy intake from food was calculated by multiplying the number of kcal provided by 100g of the specific food (kcal/100g) with the per day grams of intake and dividing by 100. This gave energy intake (kcal) per day for each specific food.

Dietary energy density was calculated by dividing energy from food by the diet weight (excluding beverages) for each participant:

Energy density (kcal/g) = Energy from food (kcal/day) / Diet weight (grams/day)

4.2.2.5.1.3 Wholegrain cereal consumption

A variable was derived for the amount of wholegrain-containing foods consumed per day for the current project. Average daily consumption of wholegrain cereals was calculated by summing the per day consumption in grams for the following food items: brown bread; wholegrain bread; shredded wheat; muesli; bran-flakes; porridge; brown rice; wholegrain pasta.

4.2.2.5.1.4 Dietary patterns

Dietary patterns were identified in sex-specific cluster analysis (PROC FASTCLUS; SAS Institute Inc, Cary, NC). Twenty-two food-frequency questionnaire items with the strongest correlation with clusters were examined to assign cluster names. Initially 6 clusters were identified: (i) very healthy, (ii) healthy (iii) Mediterranean-like, (iv) sweet; (v) unhealthy; and (vi) very unhealthy. In sex-specific cluster analysis, there was lack of concordance with the combined data, which was due largely to movement between the 2 healthy and the 2 unhealthy clusters. These were merged to yield a total of 4 clusters: (i) healthy, (ii) Mediterranean-like, (iii) sweet and (iv) unhealthy (Martikainen et al, 2003; Brunner et al, 2008). The eating pattern characterizing each cluster is given in table 4.5

Table 4.5 Description of dietary patterns obtained by cluster analysis at phase 3 of the Whitehall II study

Dietary pattern	Intake of foods compared with average intakes in the cohort
Healthy	Higher than average consumption of whole-meal bread, fruit and vegetables, and polyunsaturated margarine. Average to low consumption of red meat, sweet foods, and wine and beer.
Mediterranean-like	Higher than average consumption of whole-meal bread, fruit, vegetables, pasta and rice, and wine and beer. Low intake of full-cream milk but high intake of butter. Average consumption of white bread.
Sweet	Higher than average consumption of biscuits, cakes, meat, sausages and savoury pies, white bread, full-cream milk, butter, and wine and beer. Average intake of fruit and vegetables.
Unhealthy	Higher than average consumption of meat and sausages, white bread, fries, and full-cream milk. Average consumption of wine and beer. Very low consumption of fruit and vegetables.

4.2.2.5.1.5 Dietary misreporting

Misreporting of dietary intake is an important source of information bias in studies assessing diets with self-reported food intake, whether from diet interview, diet record or FFQ (Black et al, 1997; Westerterp & Goris, 2002). This phenomenon has been previously observed and described in the WII study (Stallone et al, 1997; Brunner et al, 2001). Misreporting of dietary intake introduces bias in the estimation of dietary exposure, distorted estimates for associations with health outcomes and incomplete adjustment when diet is treated as a control variable in multivariate modelling. In order to deal with diet misreporting, 2 new variables were derived specifically for the current project: (i) Energy intake underreporting based on the Goldberg cut-off (Black, 2000); and (ii) Ratio of energy intake to total energy expenditure (Black, 1991).

The main assumption on which identification of dietary misreporting is based is that, among individuals with stable body weight, energy intake (EI) equals total energy expenditure (TEE). The Goldberg formula (Goldberg et al, 1991) utilizes this fundamental equation of human physiology to derive cut-off values taking into account likely variation in both reported EI and estimated energy expenditure. If an EI value lies outside this range it is treated as invalid on the basis that it is implausible. The accuracy of the plausible EI values within the valid range of EI/TEE is not estimated with this method.

TEE was calculated for each participant as Basal Metabolic Rate (BMR) times the Physical Activity Level (PAL). PAL was set to 1.20 (lowest PAL that can sustain life) (WHO, 1985) for all participants. BMR was not directly measured in the Whitehall II study. Estimated BMR was calculated using the Schoefield equations based on gender and weight:

$$\text{Estimated BMR} = 11.4 \times \text{weight} + 870 \quad \text{for men}$$

$$8.1 \times \text{weight} + 842 \quad \text{for women}$$

$$\text{TEE} = \text{BMR} \times \text{PAL}$$

The Goldberg formula was then used for identifying EI intake underreporters on the basis that their reported (low) EI was unlikely to have arisen by chance. With this method, 46% men and 34% women were identified as underreporters. Since this was a large proportion of participants it was decided that exclusion of these underreporters from analysis was not a suitable way of dealing with dietary underreporting.

An approach to the problem of dietary misreporting that does not require exclusion of a large proportion of participants in epidemiological analysis, is to adjust for EI:TEE, the ratio of reported energy intake to estimated total energy expenditure. The basis of this adjustment is that those who underreport at a great extent would have a very low ratio of EI:TEE (i.e. <0.7), while the accurate reporters would be expected to have a ratio closer to 1. Adjusting for the EI:TEE variable provides estimates controlling for the fact that some participants underreport their energy intake. The EI:TEE variable was used in the current project to control for diet misreporting whenever a diet variable was used in analysis.

4.2.2.5.2 Physical activity (phase 3)

Physical activity was treated as a potential mediator in the work stressors-incident T2DM association. The phase 3 questionnaire included question items on the amount of time participants spent in mild, moderate and vigorous physical activity. This information was used to calculate MET-hours of physical activity per week. The MET values used to categorize activities were <3 METs for light, ≥ 3 – <5 METs for moderate and ≥ 5 METs for vigorous activities. One MET is the metabolic energy expended lying quietly and is equivalent to approximately 1 kcal per kilogram of body weight per hour. The MET value reflects the intensity of the activity as a multiple of one MET. Therefore, a 70-kg person walking at a moderate pace (MET value of 3.5) for 1 hour would expend 3.5 METs or 245 kcal. Total physical activity was calculated in MET-hours per week by summing the MET-hours for all three activity levels (Singh-Manoux et al, 2005).

4.2.2.5.3 Alcohol consumption (phase 3)

Alcohol consumption was treated as a potential mediator in the work stressors-incident T2DM association. At baseline and subsequent study phases, participants were asked to report the number of alcoholic drinks they had consumed in the last 7 days. This information was divided into ‘measures’ of spirits, ‘glasses’ of wine, and ‘pints’ of beer. In the United Kingdom, a standard measure of spirits, a glass of wine and a half-pint of beer are considered to contain a unit (8g) of alcohol. For the current project only the latter information was used and alcohol consumption was converted into units per week, where a unit is 8 g of alcohol. Alcohol consumption was also categorized for men and women based on the current ‘UK sensible drinking recommendations for adults in the UK’ as: no consumption; moderate consumption (1-28 units/week in men; 1-21 in women); and heavy consumption (>28 units/week in men; >21 in women) (Department of Health, 1995).

4.2.2.5.4 Smoking status (phase 3)

Smoking status was treated as a potential mediator in the work stressors-incident T2DM association. Participants were asked about their smoking status at all phases. Smoking status was categorised as never smoker; ex smoker; and current smoker. Self-reported smoking status at phase 3 was supplemented by reported smoking status data from previous phases. Participants who reported smoking at phase 3 were defined as current smokers. Those who reported not smoking at phase 3 (and were not identified as current or ex-smokers in previous phases) were classified as never smokers. Ex-smokers were those participants who reported past smoking at phase 3 or current or ex-smoking at previous phases. Around 10% of the participants at phase 3 misclassified their current smoking status as being never smokers where in fact they were ex smokers based on their previous reports.

4.2.2.6 Biological variables

4.2.2.6.1 Anthropometric (phase 3)

4.2.2.6.1.1 Height, weight and Body Mass Index

Anthropometric variables (apart from height) were treated as potential mediators in the work stressors-incident T2DM association. All anthropometric measurements were carried out according to a standard protocol (Beksinska et al, 1995). Height was measured to the nearest mm using a stadiometer with the participant standing completely erect with the head in the Frankfort plane. Weight was measured with all items of clothing removed except underwear. A Soehnle scale was used to read weight to the nearest 0.1 kg. If the reading alternated between two readings (0.1 kg apart with the participant standing still) the higher reading was recorded. Body Mass Index (BMI) was calculated as weight (kg) divided by height (m) squared. BMI is a measure of overall (generalized) obesity. A dichotomous variable for presence of obesity was created as a $BMI \geq 30 \text{ kg/m}^2$ (WHO, 1998).

4.2.2.6.1.2 Waist and hip circumferences; Waist-hip ratio and waist-height ratio

Waist circumference, Waist-hip ratio (WHR) and Waist-height ratio (WHtR) are inexpensive measures of central obesity reflecting visceral and subcutaneous accumulation of adipose tissue (Aswell et al, 1994; Kahn et al, 1994). Body circumferences were measured with participants in the standing position and unclothed, utilizing a fibreglass tape-measure at 600 g tension. Waist circumference was taken as the smallest circumference at or below the costal margin and the hip circumference at the level of the greater trochanter. WHR was calculated by dividing waist circumference with hip circumference. WHtR was developed by dividing waist circumference by height. The higher the WHR and WHtR the greater the degree of central obesity.

4.2.2.6.2 Cardiometabolic factors (phase 3)

4.2.2.6.2.1 Triglycerides and HDL-cholesterol

Cardiometabolic factors were treated as potential mediators. Serum triglycerides were measured in a centrifugal analyser by enzymic colorimetric methods. Serum cholesterol was determined by the cholesterol oxidase peroxidase colorimetric method (BCLkit;

Boehringer, Mannheim, Germany). HDL-cholesterol was determined after dextran sulphate-magnesium chloride precipitation of non-HDL cholesterol (Brunner et al, 1997).

4.2.2.6.2.2 Systolic blood pressure

Blood pressure was measured twice in the sitting position after 5 min rest with the Hawksley random-zero sphygmomanometer (Hawksley, Lancing, Sussex, United Kingdom).

4.2.2.6.2.3 Metabolic syndrome

The metabolic syndrome was based on the ATPIII definition as presence of ≥ 3 of the following: waist circumference >102 cm in men and >88 cm in women; blood pressure $\geq 130/85$ mm Hg; triglycerides ≥ 1.69 mmol/l; HDL-cholesterol ≤ 1.03 mmol/l in men and ≤ 1.29 mmol/l in women (Adult Treatment Panel III, 2002).

4.2.2.6.3 Inflammatory markers (phase 3)

4.2.2.6.3.1 Fibrinogen

Inflammatory markers were treated as potential mediators. Fibrinogen was determined by an automated modification of the Clauss clotting method using a 1:15-dilution of plasma to 0.9% saline, clotted with a half volume of bovine thrombin (50 units/ml) (Brunner et al, 1993).

4.2.2.6.3.2 C-reactive protein

CRP was measured in serum stored at -80 °C using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). Values below the detection limit (0.154 mg/l) were assigned a value of 0.077 mg/l (Brunner et al, 2008).

4.2.2.6.3.3 Interleukin-6

IL-6 was measured using a high-sensitivity ELISA assay (R & D Systems, Oxford, UK). Values below the detection limit (0.08 pg/ml for IL-6) were assigned a value equal to half the detection limit (Nabi et al, 2008).

4.2.2.6.3.4 von Willebrand factor

vWF was measured by a double-antibody ELISA with reagents provided by Dako Ltd and standards from the National Institute for Biological Standards and Control. The reference preparation and the first and second antibodies were plasma human 89/592, rabbit anti-human vWF, and Dako peroxidase-conjugated rabbit antihuman vWF, respectively (Kumari et al, 2000).

4.2.2.6.3.5 Factor VII

Factor VII activity was determined according to the method described by Brozovic et al (1974) performed without automation. A single batch of factor VII reference plasma, stored at -70°C, was obtained from a pool of normal blood donors, and was calibrated against a NIBSC standard (Brunner et al, 1993).

4.2.2.6.4 Reproductive factors (phase 3)

4.2.2.6.4.1 Menopausal status and hormone replacement therapy

Reproductive factors were treated as potential confounders. Women replied to several questions about their menstrual history at phases 3. Menopausal status was defined in the following way. Women who reported current and regular periods were defined as premenopausal. Women who reported that their period had not stopped at one phase but reported that it had by the next phase were categorized as premenopausal, as were women who reported that their periods had not stopped but that it had become less regular in the last 12 months. Women who reported that their periods had stopped were defined as

postmenopausal. Women also replied on whether they ever had hormone replacement therapy and this was used a binary variable (yes/no).

4.2.2.6.4.2 Contraceptive pill use

Women replied on a question on whether they were taking oral contraceptive pills. The variable used in the current project identifies participants as ‘ever users of contraceptive pills’ and ‘never users of contraceptive pills’ (binary variable).

4.2.3 Variable distribution

The distribution of all the variables used in the current project is presented separately among men and women in table 4.6. For continuous variables the mean and standard error are presented, while for categorical variables the prevalence is presented. The table also gives number of participants with valid information and the proportion of participants with missing information for each variable. The implications of missingness in analysis are discussed in sub-section 4.3.2.6.2.

Table 4.6 Distribution of sociodemographic, psychological, psychosocial, behavioural and biological characteristics among men and women

	MEN			WOMEN		
	% missing	N	mean (s.e) or % (N)	% missing	N	mean (s.e) or % (N)
Age (years) (phase 3)	n/a	5742	44.0 (0.08)		2579	49.8 (0.12)
Type 2 diabetes during follow-up (%) (phase 1-7)	7%	555	9,7	7%	276	10.8
Type 2 diabetes during follow-up (%) (phase 3-7)	16%	277	5,8	18%	139	6.6
Job demands scale (phase 3)	9%	5211	62.8 (0.26)	12%	2277	57.6 (0.42)
Job control scale (phase 3)	9%	5207	71.3 (0.20)	12%	2273	62.3 (0.35)
Social support at work scale (phase 3)	10%	5160	75.6 (0.24)	12%	2262	74.9 (0.40)
Job strain (%) (phase 3)	18%	1145	24.2	17%	600	31.8
Iso-strain (%) (phase 3)	18%	553	11.8	17%	283	15.1
Effort at work scale (phase 3)	9%	5201	8.96 (0.03)	12%	2273	9.50 (0.04)
Reward at work scale(phase 3)	10%	5117	29.7 (0.04)	12%	2234	29.4 (0.06)
Effort-reward imbalance scale (phase 3)	11%	5109	0.61 (0.001)	12%	2232	0.65 (0.001)
Employment grade (phase 3)	n=8			0		
High (%)		2758	48.3		404	15.7
Middle (%)		2585	45.1		1159	44.9
Low (%)		381	6.6		1016	39.4
Educational attainment (phase 5)	20%			29%		
University degree (%)		1820	39.4		481	26.4
Secondary education (%)		2522	54.6		931	51.2
No formal education (%)		276	6.0		407	22.4
Father's social class (phase 1)	7%			10%		
Non-manual (I, II, IIINM) (%)		3232	60.5		1173	50.4
IIIM (%)		1482	27.8		745	32.0
IV+V (%)		626	11.7		408	17.7
Life satisfaction scale (phase 1)	26%	5126	15.6 (0.11)	29%	2433	15.6 (0.17)
Upset by life events scale (phase 1-3)	3%	6720	2.62 (0.04)	6%	3210	3.69 (0.07)
Isolation scale (phase 1)	3%	6744	2.01 (0.02)	3%	3304	2.28 (0.02)
Anger scale (phase 1)	67%	2293	6.46 (0.09)	62%	1294	7.17 (0.13)
Hostility scale (phase 3)	34%	4539	11.0 (0.10)	40%	2033	10.8 (0.15)
Affect balance scale (phase 1)	27%	5043	3.60 (0.06)	31%	2352	2.99 (0.11)
Type A personality scale (phase 1)	3%	6725	13.4 (0.09)	6%	3227	12.8 (0.13)
Chronic GHQ scale (phase 1-3)	n=10	5732	8.59 (0.08)	n=3	2576	9.57 (0.12)
Alcohol consumption (uts/week) (phase 3)	n=7			n=2		

no (%)		840	14.6		786	30.5
moderate (%)		4243	74.0		1698	65.9
heavy (%)		652	11.4		93	3.6
Smoking status (phase 3)	2%			3%		
never (%)		2744	48.7		1408	56.2
ex (%)		2175	38.6		668	26.6
current (%)		714	12.7		431	17.2
Diet pattern (phase 3)	15%			14%		
healthy (%)		1468	30.1		826	41.9
Mediterranean-like (%)		899	18.5		382	19.4
sweet (%)		851	17.5		126	6.4
unhealthy (%)		1653	33.9		637	32.3
Dietary energy density (kcal/g) (phase 3)	1%	5699	1.17 (0.001)	n=6	2551	1.01 (0.008)
Wholegrain cereal (g/week) (phase 3)	0	5742	124.3 (1.28)	0	2579	112.5 (1.85)
EI:TEE scale (phase 3)	8%	5277	1.06 (0.001)	15%	2198	1.18 (0.007)
Physical activity (MET-hrs/d) (phase 3)	n=2	5740	3.85 (0.04)	0	2579	3.29 (0.07)
Height (cm)(phase 3)	4%	5485	176.4 (0.09)	6%	2428	161.9 (0.13)
Weight (cm) (phase 3)	4%	5490	78.1 (0.15)	6%	2428	67,2 (0.26)
BMI (phase 3)	4%	5481	25.1 (0.05)	6%	2426	25.7 (0.10)
Waist circumference (cm) (phase 3)	6%	5416	89.3 (0.13)	6%	2412	78.1 (0.25)
Hip circumference (cm) (phase 3)	6%	5414	96.7 (0.09)	6%	2412	97.1 (0.20)
Waist-hip-ratio (phase 3)	6%	5411	0.94 (0.01)	6%	2409	0.80 (0.00)
Waist-height ratio (phase 3)	6%	5405	0.51 (0.00)	6%	2411	0.48 (0.00)
Systolic blood pressure (mmHg) (phase 3)	5%	5483	121.9 (0.18)	6%	2428	117.8 (0.28)
Triglycerides (mmol/L) (phase 3)	5%	5464	1.60 (0.02)	6%	2407	1.22 (0.02)
HDL-cholesterol (mmol/L) (phase 3)	5%	5442	1.32 (0.01)	6%	2404	1.68 (0.01)
Fibrinogen (g/l) (phase 3)	11%	5104	2.34 (0.01)	11%	2289	2.59 (0.01)
C-reactive protein (mg/l) (phase 3)	9%	5209	1.79 (0.06)	12%	2272	2.25 (0.09)
Interleukin-6 (ng/l) (phase 3)	11%	5135	1.81 (0.03)	12%	2292	2.26 (0.05)
von Willebrand factor (IU/ml) (phase 3)	14%	4958	107.2 (0.57)	15%	2186	109.4 (0.89)
factor VII (IU/ml) (phase 3)	11%	5125	88.9 (0.40)	12%	2265	93.9 (0.64)
Menopause (%) (phase 3)	n/a	n/a	n/a	n=4	847	49.0
Hormone replacement therapy (%) (phase 3)	n/a	n/a	n/a	n=6	608	23.6
Contraceptive pill use (%) (phase 3)	n/a	n/a	n/a	4%	1356	52.7

A more detailed representation of the distribution of the main variables of interest as well as the variables derived for this project can be found in appendix 4.

4.3 Analysis strategy

The main aims of the current project are to investigate the independent effect and impact of psychosocial work stressors on incident T2DM and assess the contribution of biological and behavioural factors in explaining this association (chapter 3). The following steps were taken to achieve these aims, as well as specific objectives: (i) Investigation of the crude incident rate of T2DM in the WII study; (ii) Investigation of factors associated with incident T2DM in the WII study in order to identify potential confounding and mediating factors; (iii) Assessment of the effect of psychosocial work stressors on risk of T2DM adjusting for potential confounding factors; (iv) Investigation of excess risk and population impact related to exposure to psychosocial work stressors on incident T2DM among WII participants; and (v) Assessment of the effect of psychosocial work stressors on risk of T2DM adjusting for potential mediating behavioural and biological factors. Separate results chapters are addressing each analysis step mentioned above and a description of the analysis is given in the methodology section of the corresponding results chapter (chapters 5-9).

4.3.1 Standardization and test of linearity for continuous variables

Prior to the main analysis continuous variables were standardized and the linearity of their association with incident T2DM was examined.

4.3.1.1 Standardization

All continuous variables were standardized in order to aid comparisons of the effect of exposure variables on risk of T2DM. Standardization of continuous variables is a common techniques used in epidemiological studies when there is a need to compare the effect of measures with different units on an outcome. For example, instead of estimating the increase in T2DM risk per 1 cm increase in waist circumference or per 1 mmHg increase in blood pressure, with standardized variables what is estimated is the increase in disease risk per increase in 1 standard deviation of the exposure variable. Standardized

variables were computed as z-scores with mean=0 and standard deviation=1 using the STATA command *egen new_var = std(var)*. All standardized scores were sex-specific.

4.3.1.2 Departure from linearity

An assumption usually made in epidemiological studies is that for a given continuous exposure variable which is associated with a given binary outcome, the risk is increasing linearly as exposure increases. If plotted, this would present a straight line with the exposure variable in the x-axis and the risk of disease in the y-axis. However, some associations do not follow this linear fashion, but instead may be curved. Such departures from linearity can be tested using the quadratic (variable²) and cubic (variable³) terms of a given exposure variables. If these are significantly associated with the outcome of interest in a model containing the linear term of the variable then this is evidence of departure from linearity.

In the current project a test for departure from linearity was performed by creating a quadratic and cubic term for each continuous exposure variable. Models were then estimated for each continuous exposure variable with T2DM as the outcome variable, first including both the linear and quadratic term and then just the linear term. A likelihood ratio test (LRT) was used to determine whether the quadratic term significantly improved the model. The likelihood-ratio test (LRT) is based on the ratio of the maximum value of the likelihood function under one statistical model to the maximum value under a different statistical model. The two models differ in that the one includes and the other excludes one or more parameters (variables, interaction terms etc.) (Last, 2001). The null hypothesis in the LRT is that there is no difference between the two assessed models.

The quadratic term was tested for each exposure variable and if the LRT p-value was <0.05 it was concluded that the quadratic term improved the model containing just the linear term and this was taken as evidence that the association between the specific exposure and incident T2DM departed from linearity. The same procedure was followed

for investigating the effect of cubic terms. In this case, the cubic form of the variable (variable³) was introduced in a model containing the linear and quadratic form of the variable and evidence for improvement of the model was gain tested with a LRT (chapter 6).

4.4 Statistical techniques

4.4.1 Survival analysis

4.4.1.1 Description

In a cohort study participants are followed over a period of time to study the occurrence of several outcomes of interest. The advantage of cohort studies over cross-sectional or case-control studies is that they enable the researcher to calculate the incidence of a specific disease, that is the number of new cases out of the initial population at risk over a given period of time. An even more accurate approach for calculating disease incidence is by using survival analysis. This approach has the advantage of taking into account the fact that not all participants in the study are followed for the same period of time. For example participants who develop the disease of interest do not contribute to the follow-up time any more. The same applies to participants who drop out during follow-up and those deceased before the end of the follow-up time.

The time at risk for each participant is the time period from the date the participant entered the study (i.e. date of questionnaire completion or screening) until the date that the participant was diagnosed with the disease of interest or was lost to follow-up (i.e. date of missed questionnaire or screening) or deceased or until the end of the follow-up time if none of these occurred. Participants who do not develop the outcome of interest until the end of follow-up are said to be censored. For calculating incidence, adding the time at risk for all participants eligible for analysis gives total person-years at risk, which is the denominator and the number of new cases identified during follow-up is the numerator. Survival analysis is also called time-to-event analysis:

incidence (rate) = number of new cases during follow-up / total time at risk

4.4.1.2 Setting the data to survival-time

In order to use survival analysis in STATA, the **stset** command declares the data in memory to be survival-time data, creating variables for disease incidence and survival-time. In order to do this, three variables are needed: (i) a binary indicator for the presence or absence of the disease of interest during follow-up; (ii) date of entry to the study; and (iii) date of exit from the study. The syntax for the **stset** command is as follows:

stset timeout_var, fail(outcome_var) origin(timein_var) id(id_var) scale(365.25)

The **timein_var** is the date of entry, the **timeout_var** is the date of exit and the **outcome_var** is a binary variable indicating presence of the disease of interest during follow-up. The option **id** sets the identifier variable and **scale (365.25)** sets the follow up time to be in years.

In this project, the **outcome_var** is type 2 diabetes. The follow-up time for the main analysis was from 1991 (phase 3 screening) to 2004 (end of WII phase 7 screening). For investigation of the overall incidence rate of T2DM in the WII study (chapter 5), the beginning of follow-up was set to 1985 (phase 1). In the main analysis, the **timein_var** was the date of completion of the phase 3 questionnaire and the **timeout_var** was set to 30 September 2004, the closing date of phase 7, unless the participant developed T2DM during follow-up (in which case **timeout_var** was the mid-point between the date of screening of diagnosis and the date of the previous screening to diagnosis) or was lost to follow-up (in which case **timeout_var** was the date of screening at the phase in which participant did not show up). Prevalent cases of T2DM at baseline were excluded from the analysis.

4.4.1.3 Estimation of survival probabilities (chapter 5)

The survival probability is the estimated probability of *not* dying (or developing a specific disease of interest) for a randomly selected person within a specific study sample, during a specified follow-up time. An estimation of the survival probability for a specific sample of individuals can be calculated by two similar methods; The Life-table method and the Kaplan-Meier method. Both of these techniques use survival curves to plot the overall cumulative survival probability for the whole sample during the follow-up period.

The Life-table method splits the follow-up time into time intervals (usually 1 year) and calculates the probability of survival for each time interval based on the number at risk, the number diseased and the number of censored observations. This is referred to as conditional probability. Cumulative survival probabilities for each interval are calculated by multiplying the conditional probability for the specific interval with the conditional probabilities of all the preceding time intervals up to the start of follow-up.

The Kaplan-Meier method uses the same principles as the Life-table method for estimating survival probabilities but instead of using predetermined time intervals, the time intervals are determined by the time each disease event occurs. The specific time point (i.e. month and year) that each disease event occurs has to be known in order for the Kaplan-Meier method to be used. As already mentioned, for the current analysis the date of occurrence of each T2DM case was taken as the mid-point between the date of T2DM identification (screening or questionnaire) and the date of the previous assessment (screening or questionnaire). The survival curves of two groups can be compared using the Log rank test (described in the following sub-section).

For the current project, the Life-table method was used for calculating survival probabilities for each year, or a certain year-period, during follow-up (chapter 5). The Life-table was chosen for this analysis as in STATA this analysis summarizes and tabulates conditional survival probabilities for a given time period, which enables the investigation of changes in survival over time. The Kaplan-Meier method only produces

cumulative survival probabilities. The Kaplan-Meier method is more precise than the Life-table method in estimating cumulative survival probabilities, as it re-estimates the probability of surviving for every incidence of a new case. For this reason the Kaplan-Meier method was used for plotting and comparing the survival experience between categories of the main exposure variables (job strain, iso-strain and ERI) (chapter 7), as well as other exposure variables (i.e. gender, age-group, employment grade and ethnic group) (chapter 5).

4.4.1.4 Log-rank test

The log-rank test is a special form of the chi-squared test, also called Mantel-Cox chi-squared test. The log-rank test is used in survival analysis (section 4.3.3) for assessing whether the survival probability differs between two or more exposure categories. The null hypothesis is that there is no difference between the survival probabilities and any differences are due to chance. The log-rank test compares the number of observed outcome cases in each exposure category with the expected number of cases for that category.

For the current project, the log-rank test was used for comparing the survival probability by categories of several exposure variables. For example men vs. women; different age groups; and different employment grades.

4.4.1.5 Testing the proportional hazards assumption

In survival analysis, when comparing the survival probability of two or more groups (i.e. categories of an exposure variable), an assumption is made about the shape of the curve of the underlying hazard. The proportional hazards assumption concerns the survival experience (or incidence rate of disease) of two or more groups. The assumption is that the shape of the survival curves to be compared is proportional over time. When disease incidence is proportional, the hazard ratio for comparing the hazard between two (or more) groups is broadly constant over time. For example, in a 20-year follow-up, if during the first 10 years of follow-up the hazard ratio for T2DM comparing those

exposed and not exposed to work stressors is 2 and during the last 10 years of follow-up this hazard ratio rises to 4, then the hazards are not proportional over time.

In the current analysis the Schoenfeld method was used for testing the proportional hazards assumption (Schoenfeld et al, 1982). The Schoenfeld residual for work stress for each diseased person is calculated as:

Observed value (i.e. YES/NO) at time of disease (t_i) - expected value for the risk set at t_i

The expected value of work stress is the average value weighted by each individual's likelihood of being diseased at t_i .

Schoenfeld residuals are, in principle, independent of time, hence their use for testing the proportional hazards assumption. In the Schoenfeld method for testing the proportional hazards assumption, Schoenfeld residuals are plotted against follow-up time and a linear regression model estimates the association between the Schoenfeld residuals and follow-up time. A significant ($p < 0.05$) association between the Schoenfeld residuals and time means a violation of the proportional hazards assumption.

Schoenfeld residuals were plotted against follow-up time using the **stphtest** command in STATA. The slope from the regression of the Schoenfeld residuals for all the work stressor variables on follow-up time was not significant indicating that the proportional hazards assumption was not violated. Statistical textbooks highly recommend looking at survival curves (such as the Kaplan-Meier graphs) in addition to performing the statistical test for proportional hazards (Kirkwood & Sterne, 2003). From the Kaplan-Meier plot comparing incidence of T2DM between those exposed and not exposed to work stressors at analysis baseline, there was no evidence for non-proportional hazards over time.

4.4.1.6 Estimation of crude and stratified incident rates and rate ratios (chapters 5 and 7)

The incidence rate of T2DM was calculated using the STATA **strate** command. This command calculates the overall rate of T2DM with its 95% confidence intervals and the total person-years at risk. The option ‘**,per 1000**’ gives incident rate per 1000 person-years:

strate, per 1000

Stratified incident rates were calculated by adding a specific exposure variable to the model. For example:

strate agegroup , per 1000

This rate ratio represents the ratio of T2DM incidence in a given exposure category to the incidence in the reference exposure category. Graphs were constructed in Microsoft Excel displaying the change in incident rate of T2DM both yearly and in time periods during follow-up.

4.4.1.7 Missing information during follow-up

4.4.1.7.1 Loss to follow-up

4.4.1.7.1.1 Study baseline (phase 1) to analysis baseline (phase 3)

At study baseline (1985-88), 10 308 men and women participated in the study. From these participants 8129 (79%) participated at phase 2 and 8808 (85% of initial sample) participated at phase 3. The 1500 non-participants were initially invited to participate at phase 3 and either refused to participate, did not show up in the screening clinic, were not employed at civil service any more or they were deceased before the time of screening. Table 4.7 below displays some key characteristics for those lost to follow-up from phase 1 to phase 3 and those who participated at phase 3.

Table 4.7 Distribution of main variables of interest among those who participated at Whitehall II phase 3 (1991-93) and those lost to follow-up from study baseline (1985-88) up to phase 3

	Participated at phase 3 (N=8807)		Lost to follow-up (N=1501)		<i>p</i> for difference
Women (%)	2752	31.3	661	44.0	<0.001
Age mean (s.e)	8807	44.4 (0.06)	1501	44.8 (0.16)	0.03
Employment grade (study baseline) %					
High	2746	31.2	282	18.8	
Middle	4307	48.9	637	42.4	
Low	1755	19.9	582	38.8	<0.001
job strain (study baseline) %	1888	21.7	350	23.8	0.08
iso-strain (study baseline) %	870	10.1	181	12.4	0.006
effort-reward imbalance mean (s.e)	7558	0.25 (0.01)	1243	0.25 (0.01)	0.93
BMI mean (s.e)	6786	24.5 (0.04)	2008	24.9 (0.09)	<0.001

Table 4.7 shows some evidence of selection bias due to non-random drop out from the study at phase 3. Participants who dropped out were more likely to have reported iso-strain at phase 1, and such bias could lead to a type II error or underestimation of the size of effect. Also, participants who dropped out had relatively adverse characteristics in terms of SEP (employment grade) and degree of obesity.

4.4.1.7.1.2 Phase 3 to phase 7

From phase 3, 2013 participants were lost to follow-up up to phase 7 (2002-04). This is 30% of the 8808 who participated at phase 3. The reasons for loss to follow-up from phase 3 to phase 7 are the same as described above for phase 1 to phase 3. Some key characteristics of the participants lost to follow-up from phase 3 to phase 7 compared to those who participated at phase 7 is given in table 4.8.

Table 4.8 Distribution of main variables of interest among those who participated at Whitehall II phase 7 (2002-04) and those lost to follow-up from phase 3 to phase 7

	Participated at phase 7 (N=6795)		Lost to follow-up (N=2013)		<i>p</i> for difference
Women (%)	1959	29.7	620	35.8	<0.001
Age mean (s.e)	6795	49.5 (0.07)	2013	50.5 (0.14)	0.03
Employment grade (study baseline) %					
High	2698	41.0	474	27.5	
Middle	2997	45.5	747	43.2	
Low	891	13.5	506	29.3	<0.001
job strain (study baseline) %	1341	25.6	404	29.3	0.005
iso-strain (study baseline) %	634	12.2	202	14.8	0.011
effort-reward imbalance mean (s.e)	5860	0.62 (0.01)	1481	0.64 (0.01)	<0.001
BMI mean (s.e)	6387	25.2 (0.05)	1688	25.7 (0.10)	<0.001

Table 4.8 shows that compared to those who participated up to phase 7, participants who dropped-out from phase 3 to phase 7 were more likely to come from the lower employment grades and to have higher levels of obesity.

4.4.1.7.2 Missing/incomplete data

At each data collection phase information was missing for some of the variables. Missing data were identified as: (i) information missing or incomplete (the participant did not answer the questions or did not undergo specific screening in clinic); OR (ii) the information provided by the participant (or collected by the clinic nurse) is invalid (i.e. impossible weight, blood pressure etc.). The proportion of participants with missing information for all variables used in the current project is presented in table 4.6.

The proportion of participants with missing information on incidence T2DM during follow-up was 16% for men and 18% for women of those who participated in the phase 3 screening. Participants with missing values on incidence of T2DM are those participants who neither answered any of the questions on doctor-diagnosed diabetes or use of diabetes medication nor had a screening examination for diabetes (OGTT or fasting).

For psychosocial work stressors, the proportion missing were 9% for men and 12% for women for job demands, 9% for men and 12% for women for job control, 10% for men and 12% for women for work social support, 18% for men and 17% for women for job strain, 18% for men and 17% for women for iso-strain, 9% for men and 12% for women for effort at work, 10% for men and 12% for women for reward at work and finally 11% for men and 12% for women for ERI. A missing value on the work stressors measures could indicate that the participant: (i) did not complete the phase 3 questionnaire; (ii) gave no data or incomplete data on the work stress questions at phase 3; or (iii) was not in employment at phase 3.

Apart from the main variables of interest, the variables with a large proportion (>20% missing) of missing information were educational attainment (20% men, 29% women) and the anger scale (67% men, 62% women). The missingness in these two variables did not eventually affect the results as these variables were not chosen as potential confounders as they were not associated with incident T2DM (chapter 6) and thus were not included in the main analysis of the project.

4.4.1.7.3 Excluded participants

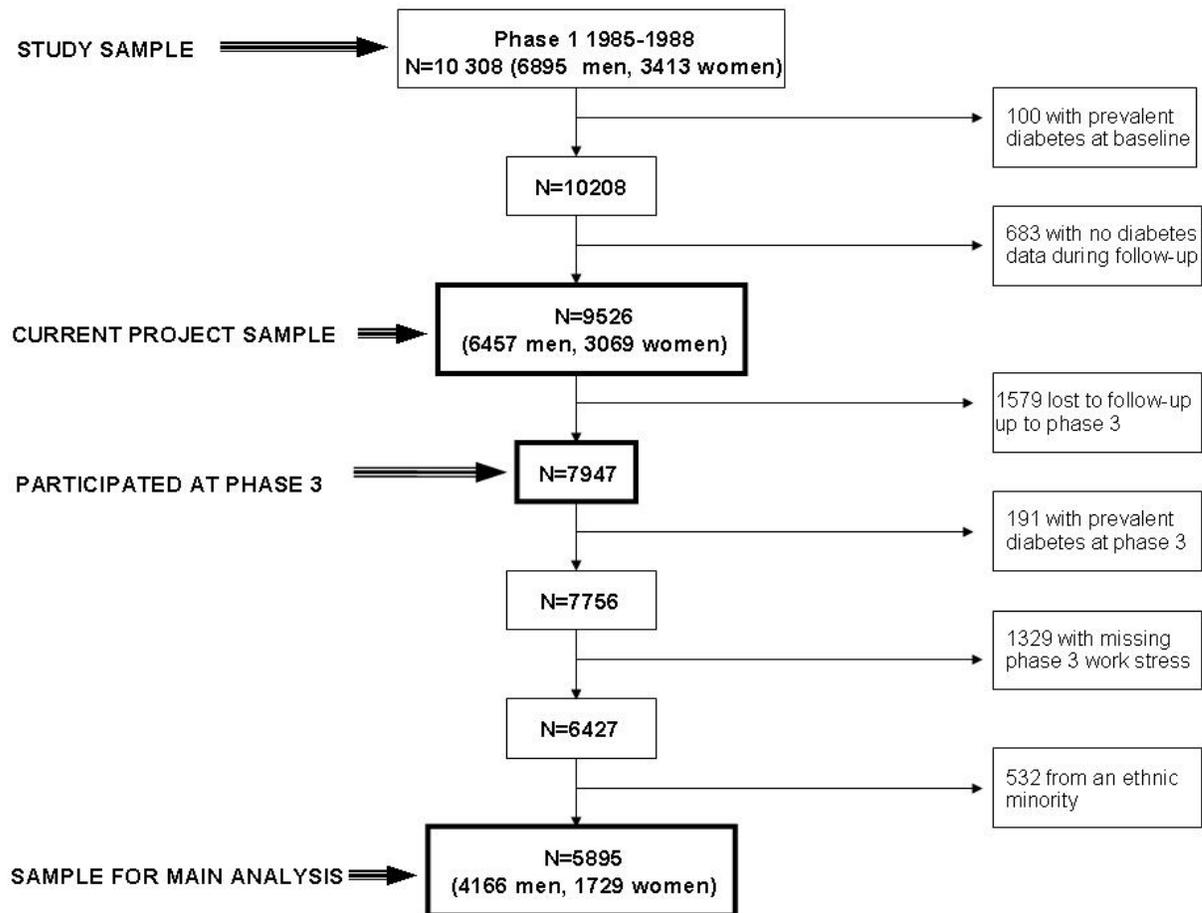
Participants were excluded: (i) when data on the main exposure and/or outcome variables were missing (section 4.3.2.6.2); and (ii) as a way of dealing with potential confounding by ethnic minority participants.

Participants were excluded if there was no information on diabetes status during follow-up (N=683). Participants with missing, incomplete or invalid information on all three psychosocial work stressor variables used (job strain, iso-strain and ERI) at phase 3 (N=1329) were also excluded from analysis.

The main analysis was restricted to Caucasian participants. Ethnic minorities were however included in the investigation of overall T2DM incidence in the WII study (chapter 5), but due to the small number of these participants and the potential for

confounding the main association, it was decided to exclude ethnic minorities from subsequent analysis. Participants from an ethnic minority group at phase 3 (N=532) were thus excluded from analysis looking at the effect of work stressors on incident T2DM. Several studies investigating risk factors for T2DM among ethnic minority groups confirm that the effect of risk factors on T2DM (as well as CVD) differs substantially between different ethnic groups (Kurian & Cardarelli, 2007). A good example is abdominal obesity as a risk factor for diabetes, where it has been shown that for the same waist circumference, Asian participants have more intra-abdominal fat and higher T2DM risk compared to whites and hence the different cut-off points for identifying central obesity based on waist circumference (≥ 94 in Europeans compared to ≥ 90 in S.Asians) (IDF, 2005). Figure 4.12 displays the specific sample for the main analysis after loss to follow-up and exclusions.

Figure 4.12 Whitehall II study sample and the sample selected for analysis in the current project after loss to follow-up and exclusion criteria



4.4.2 Cox proportional hazards regression (chapters 6-9)

Cox proportional hazards regression analysis was used for the main analysis of the current project (chapters 6-9). The Cox proportional hazards regression technique is a survival analysis technique developed by D.R Cox in 1972. The principles of the technique are similar to those of logistic regression. The only main difference is that the Cox regression model includes a function for time. Cox proportional hazards regression can be used for estimating the cumulative baseline hazard ratio for a given exposure variable.

4.4.2.1 Cox regression models (chapters 6-9)

The Cox regression model is given by the formula:

$$h(t) = h_0(t) * \exp(\beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \dots + \beta_nx_n)$$

where $h(t)$ is the hazard (risk) at time t , $h_0(t)$ is the baseline hazard (the hazard for an individual in whom all exposure variables=0) at time t and x_1 to x_p are the exposure variables 1 to n.

For a model with just a single binary exposure the hazard ratio at time t is given by:

$$HR(t) = h_0(t) * \exp\beta_1 / h_0(t) = \exp(\beta_1)$$

The estimate $\exp(\beta_1)$ is the hazards ratio. The model assumes that the hazard ratio remains constant over time. This is the proportional hazards assumption explained in sub-section 4.3.2.4

In STATA, the **stcox** command uses Cox proportional hazards regression to estimate hazard ratios for multiple exposures on a given outcome over a specified follow-up time. In order to use the **stcox** command the data have to be set to survival-time (sub-section 4.3.2.2). By default, the command **stcox** uses the Breslow's method for handling ties and presents results as exponentiated hazard ratios.

For categorical exposure variables, a heterogeneity p-value provides evidence for the overall association between the exposure variable and incident T2DM in Cox regression analysis. The hazard ratios presented in the tables (chapters 6-9) represent relative risks for T2DM for each category of exposure (if the exposure variable is categorical). For ordered categorical exposures, a trend p-value was calculated by including the categorical variable as a linear term in the model. Finally, for continuous variables, the hazard ratios represent the increase in disease risk per increase in 1 standard deviation of exposure. In

Cox regression, as with all the other techniques, a p-value of <0.05 was taken as evidence for an association.

4.4.2.2 Backwards modelling (chapter 6)

Backwards modelling refers to a comparison of consecutive multivariate regression models with the removal of a variable each time the model is estimated. After each removal the likelihood ratio test (sub-section 4.3.1.2) was used for statistically comparing the difference in the strength of the model containing the more variables to the one containing one less variable. Backwards modelling was used in addition to multivariate Cox regression analysis as an alternative in helping identify factors associated with incident T2DM (chapter 6).

4.4.2.3 Tests for interaction (chapter 7)

Interaction between two exposure variables is said to exist when the association between an exposure variable and an outcome variable is modified by another variable. In other words, the effect of an exposure variable on an outcome variable is different for each category of a third variable. For this reason statistical interaction is also called effect modification (the latter term used more in experimental studies). The likelihood ratio test was used as a statistical test for interaction by comparing a model with an interaction term between two variables (i.e. *regress outcome_var exposure_var*sex*) and comparing this with the same model without the interaction term. The null hypothesis in this statistical test is that there is no interaction between the variables. A p-value <0.05 thus provides evidence for the existence of an interaction between two variables in their association with the outcome of interest (chapter 7).

4.4.3 Receiver Operating Characteristic analysis (chapter 6)

Receiver Operating Characteristic (ROC) analysis is usually used for assessing the agreement of diagnostic tests against a gold standard or the ability of diagnostic tests in identifying diseased cases by producing ROC curves of sensitivity vs. 1-specificity.

Sensitivity is the proportion of true positives correctly identified by the test (exposure) variable. Specificity is the proportion of true negatives correctly identified by the test variable. ROC analysis can also test the overall ability of continuous measures to discriminate between diseased and non-diseased individuals. The area under the ROC curve (AUC) provides an estimate of the predictive power of a variable or model in identifying disease cases. The larger the area under the ROC curve the greater the predictive power of the variable or model. An AUC of 1 means perfect prediction, while an AUC of 0.5 means zero prediction. The AUC represents the probability that a randomly selected case will have a score greater than a randomly selected non-case. ROC analysis can test the equality of 2 or more AUCs with a statistical test. The AUC can be compared for individual variables as well as for regression models containing several variables. For comparing models, the regression model is estimated and the residuals for the specific model are saved as a new variable. ROC can then identify the model with the best predictive power. The p-values given by the ROC analysis represent evidence against the null hypothesis of no difference in predictive power between different variables or models. A p-value of <0.05 is taken as evidence that one (or more) variable(s) predict disease cases better than the others.

In STATA the **roccomp** command tests the differences between ROC areas and plots the ROC curves. In this project ROC analysis was used to compare the predictive power of alternative obesity measures in identifying incident T2DM cases.

4.4.4 Calculation of absolute risk (chapter 8)

In order to calculate absolute risk of T2DM by baseline exposure to psychosocial work stressors, the following measures were used: (i) attributable risk; (ii) attributable fraction for exposed; (iii) population attributable risk; and (iv) population attributable fraction.

Attributable risk (AR) is the absolute difference between two rates. The attributable risk was calculated as the difference between the rate in those exposed to work stressors and those unexposed:

$AR = \text{Rate in exposed} - \text{Rate in unexposed}$

Attributable fraction for exposed (AF) is the proportion of cases in the exposed group that are attributed to the exposure, assuming a causal association. The attributable fraction was calculated as:

$AF = \text{Attributable risk} / \text{Rate in exposed}$

Attributable risk and attributable fraction are considered measures of excess risk among the exposed.

Population attributable risk (PAR) is the absolute difference between the rate in the whole study population and the rate in the unexposed group. The population attributable risk was calculated in the following way.

$PAR = \text{Rate in whole sample} - \text{Rate in unexposed}$

Population attributable fraction (PAF) is the proportion of all cases in the whole study population that may be attributed to the exposure, on the assumption of a causal association. The population attributable fraction was calculated in the following way.

$PAF = \text{Population attributable risk} / \text{rate in the whole sample}$

Population attributable risk and population attributable fraction are considered as measures of population impact.

4.4.5 Assessment of mediation (chapter 9)

In order to examine the proportion of potential effect of psychosocial work stressors on incident T2DM explained by mediating variables, the observed effect after adjustment for potential confounders (socioeconomic, psychosocial and psychological factors) was

further adjusted for potential mediators (behavioural and biological factors). After estimating these 2 models, the following formula was used for calculating proportion of effect explained by mediators (Rothman, 1998; Chandola et al, 2008):

$$\frac{HR \text{ adjusted for potential confounders} - HR \text{ adjusted for potential confounders} + \text{mediator(s)}}{HR \text{ adjusted for potential confounders} - 1}$$

4.5 Estimation of study power

The power of a study is the probability that the particular study detects the ‘true’ effect of an exposure variable on an outcome variable (Kirkwood & Sterne, 2003). The power of a study depends on the sample size, on the expected effect and on the required significance level. Power calculations are essential in demonstrating that a particular study is capable of answering the questions posed and test the hypotheses initiated by the researchers. A low study power may lead to type II errors (failure to reject null hypothesis when null hypothesis is wrong).

For the current project, power calculations were conducted in order to estimate the study power for the hazard ratio for T2DM by baseline (phase 3) job strain, iso-strain and ERI among men and women. In addition, calculations were conducted in order to estimate the study power for investigation of the effect of work stressors (calculated only for iso-strain) within categories of employment grade and obesity. Even though more stratified analyses were conducted, power calculations were restricted to the ones mentioned as these were the major effect modifications assessed.

In STATA, the command **powercal** can be used for calculating the study power. In order for STATA to calculate the study power with the powercal command the following have to be given: (i) the expected effect estimate; (ii) the standard error of the effect; (iii) the significance level of choice; and (iv) the number of categories in the exposure variable. The study power is then given as a new variable in the dataset. The procedure followed was first to estimate a model with the psychosocial work stressor as the exposure variable

and incident T2DM as the outcome variable in order to obtain the expected estimates (hazard ratio and standard error). Then the 'powercal' command was used to calculate the study power for each specific model. As an effect was only apparent among women (chapter 7), the expected effect for men was set to the effect size observed among women. The significance level was set to 5%. The number of exposure categories was 2 (i.e. exposed to work stressors vs. not exposed). The same procedure was followed for calculation of study power within strata of employment grade and obesity. Both employment grade and obesity were categorised as binary variables in order to test their interaction with work stressors. For example, what is the study power for finding an effect of a certain magnitude among obese women in the current sample? This and other power calculations for the current project are presented in table 4.9

Table 4.9 Estimated study power for the main expected findings of the project

Estimate	Expected effect	Standard error	N	Significance level	Power
<i>MEN</i>					
Effect of job strain on incident T2DM	1.6	0.14	3726	5%	100%
Effect of iso-strain on incident T2DM	1.8	0.22	3698	5%	100%
Effect of ERI on incident T2DM	2.4	0.29	3824	5%	100%
Effect of iso-strain on incident T2DM among MIDDLE/HIGH GRADE participants	3.5	0.25	3757	5%	100%
Effect of iso-strain on incident T2DM among LOW GRADE participants	1.6	0.31	216	5%	23%
Effect of iso-strain on incident T2DM among NON-OBESE participants	1.4	0.23	3423	5%	100%
Effect of iso-strain on incident T2DM among OBESE participants	2.7	0.39	262	5%	100%
<i>WOMEN</i>					
Effect of job strain on incident T2DM	1.6	0.34	1479	5%	99%
Effect of iso-strain on incident T2DM	1.8	0.47	1472	5%	97%
Effect of ERI on incident T2DM	2.4	1.46	1573	5%	100%
Effect of iso-strain on incident T2DM among MIDDLE/HIGH GRADE participants	3.5	2.89	1039	5%	90%
Effect of iso-strain on incident T2DM among LOW GRADE participants	1.6	0.44	563	5%	33%
Effect of iso-strain on incident T2DM among NON-OBESE participants	1.4	0.50	1261	5%	80%
Effect of iso-strain on incident T2DM among OBESE participants	2.7	1.00	211	5%	77%

Table 4.9 indicates that there is adequate power to estimate an effect of psychosocial work stressors on incident T2DM in the magnitude of around 1.5-2.5 in both men and women, which is the main finding sought in the current project. In addition there is adequate power to estimate the effect of work stressors within categories of other variables (employment grade and obesity) apart from specific cases where power is low. Power is low for testing the effect for iso-strain on incident T2DM among low grade men and women (power= 23% and 33% respectively for an expected relative risk of 1.6). Apart from these 2 cases, the sample used for the main analysis in the current project provides enough power for generating evidence on the overall association between 3 work stressors and incident T2DM among men and women and for assessing potential interactions between work stressors and other variables in relation to T2DM risk.

The following 4 chapters (chapters 5-9) present the results of the current project on the effect and impact of work stressors on incident T2DM and the mechanisms involved. Chapters 7-9 are addressing the main aims of the project (see chapter 3), while chapters 5 and 6 help to generate evidence on the overall T2DM incidence and factors associated with T2DM, respectively, in the WII study.

Chapter 5: Incidence rate of type 2 diabetes in the Whitehall II study - Survival analysis

5.1 Introduction

The global prevalence of diabetes mellitus is increasing (King et al, 1998; Wild et al, 2004). In the UK, prevalence of T2DM increased in men from 2.9% in 1994 to 3.3% in 1998, to 4.8% in 2003 among men and from 1.9% to 2.5% and 3.6% respectively among women (Sporston & Primatesta, 2003). Prevalence of a disease depends on the incidence rate and on the death rate associated with the specific disease. The death rate associated with T2DM is relatively low and is decreasing over the years due to medical advances mainly in screening and glucose regulation (Thomas et al, 2003; Tierney et al, 2004; Charlton et al, 2008). Therefore it cannot be said with certainty whether the observed increase in global prevalence is due to an increase in the incidence rate of the disease. In the UK, prior to the 1999 change in the WHO diagnostic criteria for diabetes, it was estimated that over 98 000 new T2DM cases were diagnosed each year (Gatling et al, 2001). The incidence rate of T2DM in selected countries is presented in table 5.1.

Table 5.1 Incidence rate of type 2 diabetes and change in incidence over time in selected countries

Country	Age-group	Period	Incidence rate	Change over time	Reference
England	≥30	1996-1998	1.9 per 1000 persons per year	n/a	Gatling et al, 2001
Scotland	≥35	1993-2004	2.6 per 1000 persons per year	increased	Evans et al, 2007
Sweden	35-79	1972-2001	3.0 per 1000 persons per year	constant	Jansson et al, 2007
Denmark	40-70	1995-2006	3.0 per 1000 persons per year	increased then stabilised	Carstensen et al, 2008
Holland	20-69	1998-2000	2.3 per 1000 persons per year	n/a	Ubink-Veltmaat et al, 2003
Greece	32-59	1992-1997	11.0 per 1000 persons per year	n/a	Panagiotakos et al, 2008
U.S.	≥18 years	1984-1992	2.4 per 1000 persons per year	n/a	Ford et al, 1997

The WII study has a unique dataset with repeated clinical ascertainment of diabetes for over 20 years of follow-up. The incidence rate of T2DM has not been investigated before in this sample of male and female middle-aged civil servants. Investigation of the incident rate of T2DM will help determine the similarities of the current sample with the general UK population in terms of incidence of T2DM and also determine whether the increase in rate reported in other studies and surveys is also apparent in WII. In addition, investigation of stratified incident rates for selected sociodemographic variables would help identify groups of participants more affected by the disease. It has been previously shown in the UK that diabetes affects older ages, is higher the lower the SEP and affects minority ethnic groups more than whites (Sporston & Primatesta, 2003).

5.2 Chapter aim, objectives and main hypotheses

Aim: To determine crude and stratified incidence rates and rates ratios for T2DM, as well as change in these rates over time, in the Whitehall II study.

Objectives:

1. To calculate and plot crude and stratified cumulative survival probabilities for T2DM from WII phase 1 (1985-88) to phase 7 (2002-04).
2. To determine the crude prevalence and crude and stratified incidence rate of T2DM from WII phase 1 (1985-88) to phase 7 (2002-04).
3. To investigate the change in crude T2DM incidence rate over time during follow-up

Main hypotheses:

1. The incident rate of T2DM in the Whitehall II study is similar to other studies in Western European populations.
2. The incident rate of T2DM is higher in older ages, lower employment grades and ethnic minority groups.
3. The crude incidence rate of T2DM increases over time in the Whitehall II study.

5.3 Chapter sample and methodology

5.3.1 Sample description

The baseline for this analysis was phase 1 of the WII study. For a detailed description of follow-up in the WII study refer to methods chapter, section 4.1. The specific sample used in the current chapter is displayed in figure 4.2 in the methods chapter. The participants included for analysis in the current chapter were participants free from diabetes at study baseline (phase 1) and who had follow-up data on blood glucose levels or self-reported diabetes at least in one of the subsequent six follow-up phases up to phase 7. The participants included for analysis were 5698 men and 2560 women (total n=9525).

5.3.2 Variables used

The variables used in the current chapter, together with the sub-section in which they were described in the methods section, are listed below:

- Incident T2DM (4.2.2.1)
- Age (4.2.2.3.2)
- Employment grade (4.2.2.3.2)

5.3.3 Statistical analysis

Survival analysis was used to determine the incidence rate of T2DM in the WII study over the period 1985 (beginning of phase 1) to September 2004 (end of phase 7). Detailed description of survival analysis can be found in the methods chapter, section 4.3.2.

5.3.3.1 Estimation of crude and stratified survival probabilities

Estimation of conditional and cumulative survival probabilities was described in methods chapter, sub-section 4.3.2.3. Survival probabilities were plotted and tabulated over the whole follow-up time. In addition, Kaplan-Meier curves (sub-section 4.3.2.3) were used to graphically present the survival experience of the sample for T2DM incidence.

Survival curves were also stratified by gender, age group (39-44/45-49/50-54/55-63), employment grade (high/middle/low) and ethnic group (European/South Asian/Black/other). The survival probability between exposure categories were compared using the Log rank test (sub-section 4.4.1.4).

5.3.3.2 Estimation of crude and stratified incidence rates

Detailed description on the calculation of incidence rates of T2DM and change in rate over time can be found in the methods chapter (sub-section 4.3.2.5). Both crude and

stratified incidence rates were calculated. Stratified incidence rates were calculated for gender, age-group, employment grade and ethnic group.

For investigating change in rate over time, the incidence rate of T2DM for each year of follow-up was calculated by dividing the number of T2DM cases for each year with the number at risk at the beginning of each year. Incidence rates were also calculated for three consecutive time periods by dividing the follow-up time in 3 periods. In this way a clearer picture of change in rate over time was given as each time period included a wave (phase) of questionnaire ascertainment and one wave of clinical screening for T2DM. The first period included cases from phases 2 and 3, the second period from phases 4 and 5 and the third period from phases 6 and 7. The average incidence rate per year for each period was calculated by dividing the overall incidence rate for each 7-year period by 7.

5.4 Baseline characteristics

Baseline sociodemographic characteristics of the participants included in analysis for the current chapter, based on their diabetes status during follow-up are presented in table 5.2.

Table 5.2 Sociodemographic characteristics of participants in the Whitehall II baseline (1985-88) by follow-up diabetes status

	Diabetes during follow-up (N=922)	No diabetes (N=8605)
Women%	29.9 (276)	26.5 (2284)
Age group%*		
39-44	20.7 (191)	28.3 (2434)
45-49	20.1 (185)	26.6 (2286)
50-54	23.4 (216)	20.0 (1720)
55-63	35.8 (330)	25.2 (2165)
Employment grade%*		
High	22.1 (204)	31.2 (2687)
Middle	50.2 (463)	48.3 (4155)
Low	27.7 (255)	20.5 (1763)
Ethnic group%*		
European white	84.1 (775)	94.8 (8153)
S.Asian	9.4 (87)	2.5 (212)
Black	4.7 (43)	1.8 (157)
Other	1.8 (17)	1.0 (82)

*p<0.05

Table 5.2 shows that compared to participants with no diabetes, participants diagnosed with T2DM during follow-up were older and more likely to come from the lower employment grade and from an ethnic minority (all p-values <0.05).

5.5 Cumulative survival probability

The total follow-up time was 428 053 person-years from 1985 to 2004. The maximum time at risk was 21.5 years and the mean follow-up time was 16.4 years. During follow-up, 922 new T2DM cases were identified. Cumulative survival probabilities for T2DM in the current sample are presented in table 5.3.

Table 5.3 Cumulative survival probabilities (95% Confidence Intervals) for type 2 diabetes during a 21 year follow-up in the Whitehall II study

Time interval (years)	Participants at risk	T2DM cases	Censored	Cumulative survival probability	95% CI
0-1	9527	3	0	0.9997	0.9990-0.9999
1-2	9524	24	35	0.9972	0.9959-0.9981
2-3	9465	10	161	0.9961	0.9946-0.9972
3-4	9294	12	99	0.9948	0.9931-0.9961
4-5	9183	82	139	0.9858	0.9832-0.9881
5-6	8962	72	104	0.9779	0.9747-0.9807
6-7	8786	65	69	0.9707	0.9670-0.9739
7-8	8652	27	225	0.9676	0.9637-0.9710
8-9	8400	15	217	0.9658	0.9619-0.9694
9-10	8168	30	195	0.9622	0.9581-0.9660
10-11	7943	73	98	0.9533	0.9487-0.9575
11-12	7772	93	99	0.9418	0.9367-0.9466
12-13	7580	28	45	0.9383	0.9331-0.9432
13-14	7507	22	183	0.9356	0.9302-0.9406
14-15	7302	39	174	0.9305	0.9249-0.9357
15-16	7089	77	94	0.9203	0.9143-0.9259
16-17	6918	118	195	0.9044	0.8978-0.9106
17-18	6605	81	94	0.8932	0.8863-0.8998
18-19	6430	41	2167	0.8864	0.8792-0.8932
19-20	4222	10	2453	0.8834	0.8760-0.8904
20-21	1759	0	1734	0.8834	0.8760-0.8904
21-22	25	0	25	0.8834	0.8760-0.8904

Table 5.3 shows the survival experience of the whole sample for each consecutive year during follow-up. As expected, the cumulative survival probability decreases as more T2DM cases are identified during follow-up. There are some periods with a substantially higher number of incident T2DM cases. These periods are between 4-7 years, between 10-12 years and between 15-18 years. As mentioned previously, T2DM was ascertained both with a clinical assessment (OGTT and fasting glucose) and with a questionnaire depending on the study phase. Also, the specific date of T2DM identification was taken as the mid-point between screening identification and the date of the previous screening wave. The periods with the higher incidence of T2DM observed in table 5.2 are the mid-point periods between phase 3 screening and phase 1; phase 5 screening and phase 3

screening; and phase 7 screening and phase 5 screening. As expected, identification of cases during these screenings was higher as it was based both on self-reports and clinical assessment.

Figure 5.1 shows graphically the cumulative survival probability during follow-up. The subsequent figures 5.2-5.5 show survival probabilities stratified by specific sociodemographic characteristics.

Figure 5.1 Cumulative survival probabilities for type 2 diabetes during 21 years of follow-up using the Kaplan-Meier method in the Whitehall II study

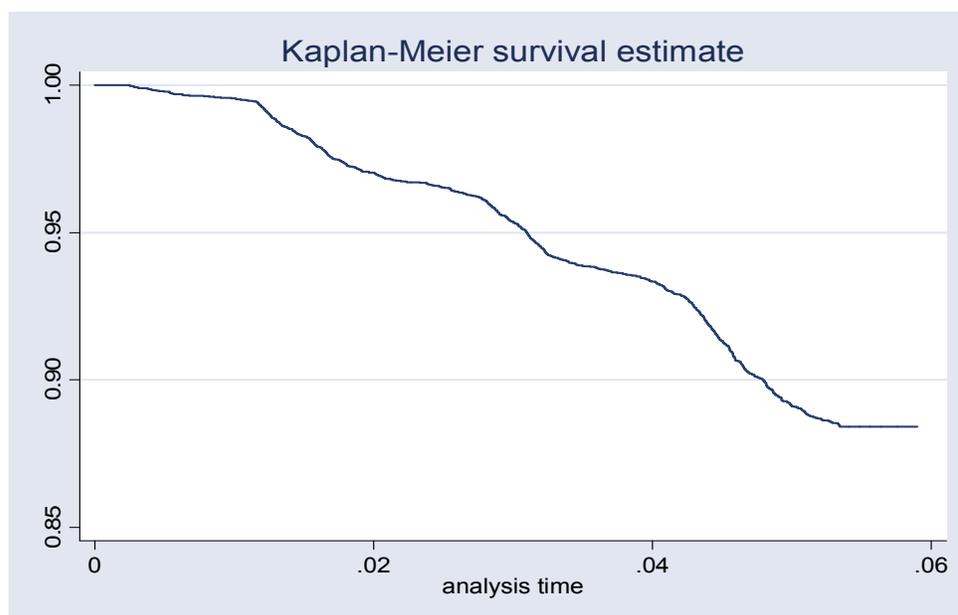
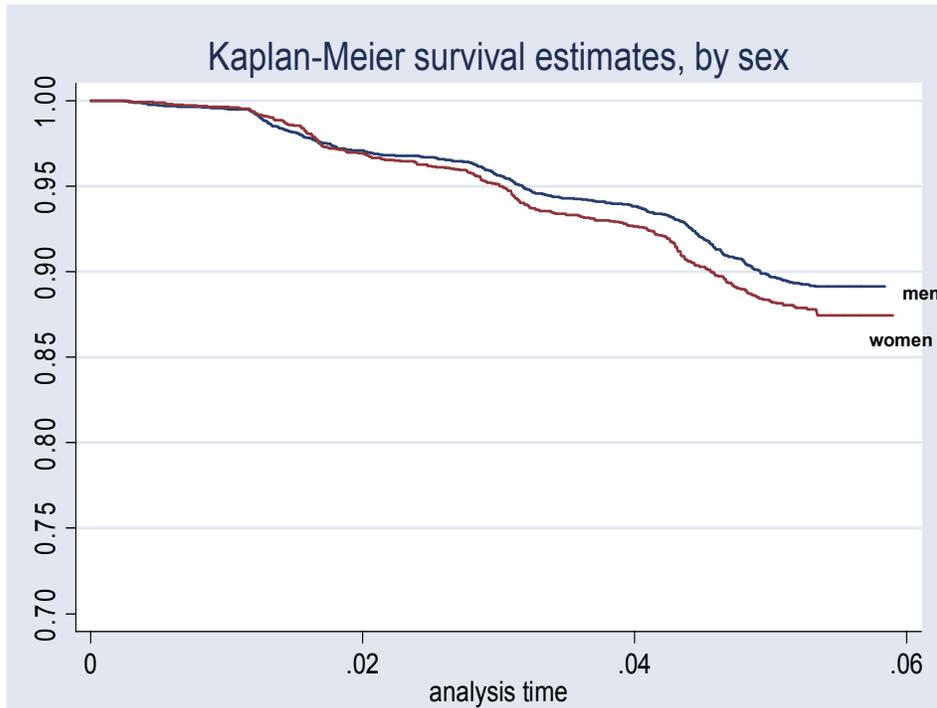


Figure 5.1 shows the reduction in the overall survival probability for incident T2DM in the WII study, from phase 1 to phase 7. Beginning with a sample free from diabetes in 1985, the survival probability (i.e. probability of not developing diabetes) decreased linearly with follow-up time up to 2004.

Figure 5.2 Cumulative survival probabilities for type 2 diabetes during 21 years of follow-up using the Kaplan-Meier method in the Whitehall II study by gender



men v. women Log-rank $p=0.051$

Figure 5.2 shows that the cumulative T2DM survival probability is lower in women than in men. In other words, overall, women were marginally less likely to remain free of T2DM compared to men during follow-up (log-rank test $p=0.051$).

Figure 5.3 Cumulative survival probabilities for type 2 diabetes during 21 years of follow-up using the Kaplan-Meier method in the Whitehall II study by age-group

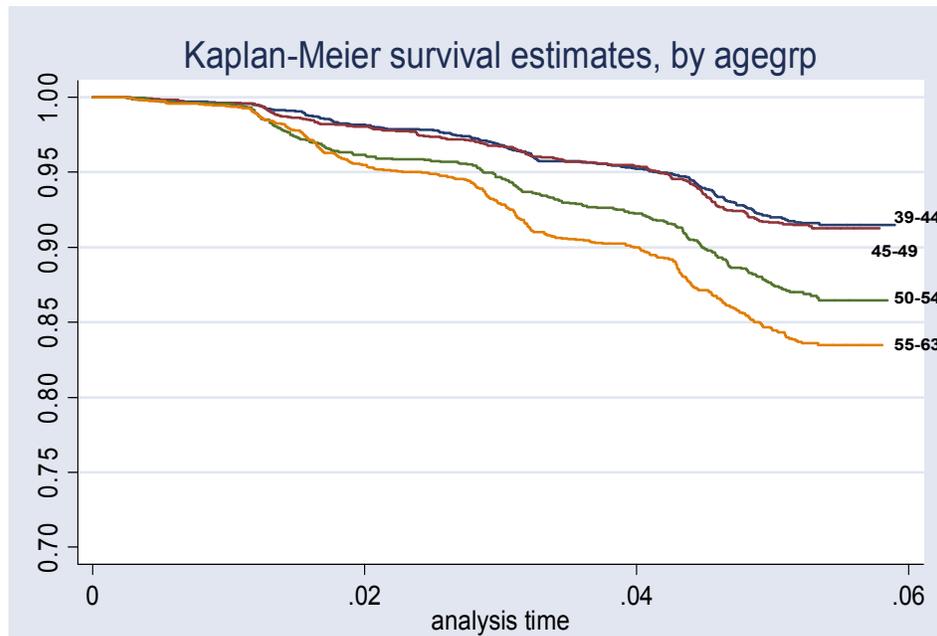
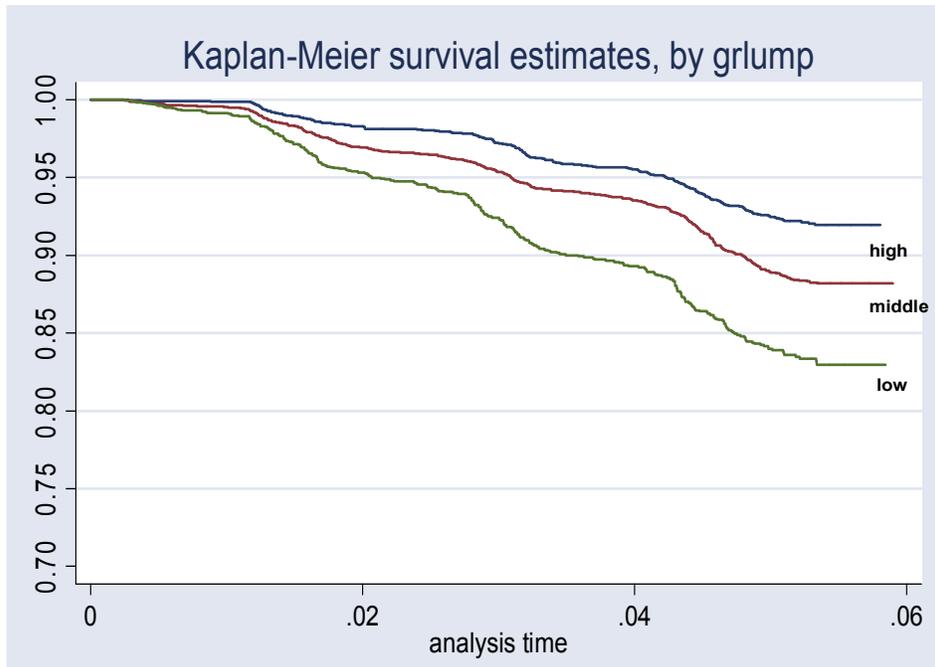


Figure 5.3 shows that the survival probability for T2DM decreased significantly with increasing baseline age group (apart from the age-group 45-49). The younger participants, at baseline, were more likely to survive from diabetes during follow-up. This was expected given that T2DM is a degenerative disease which increases by increasing age.

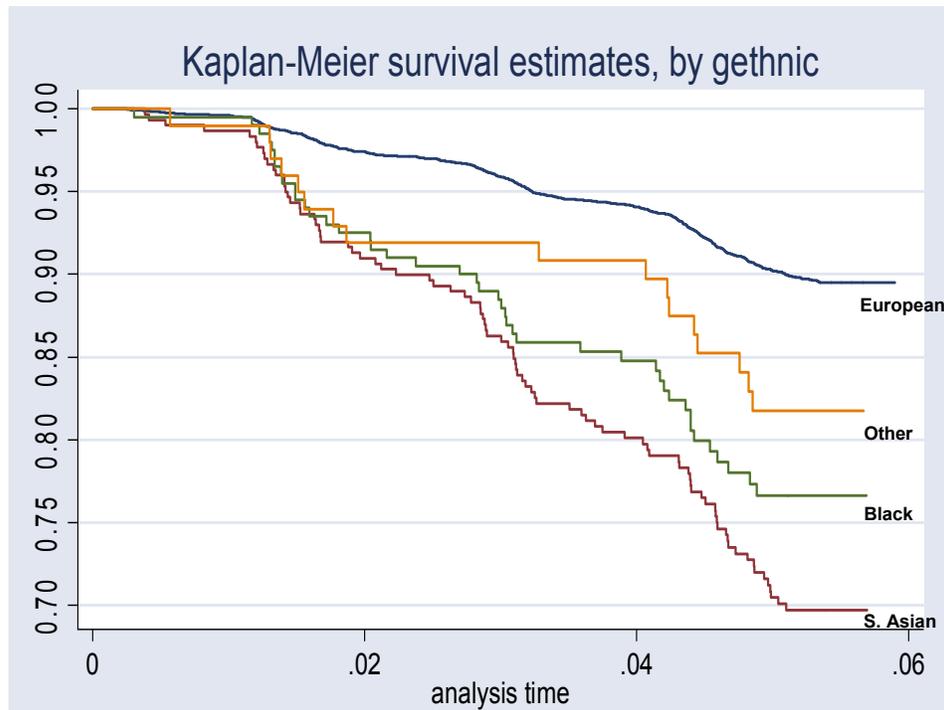
Figure 5.4 Cumulative survival probabilities for type 2 diabetes during 21 years of follow-up using the Kaplan-Meier method in the Whitehall II study by employment grade



Log-rank $p < 0.001$

Figure 5.4 shows that the survival probability for T2DM decreased significantly with decreasing employment grade. The probability of *not* developing diabetes decreased linearly from high employment grade to middle grade to low grade. This indicates that incidence of T2DM is socially patterned in the WII study, as in the general population.

Figure 5.5 Cumulative survival probabilities for type 2 diabetes during 21 years of follow-up using the Kaplan-Meier method in the Whitehall II study by ethnic group



Log-rank $p < 0.001$

Figure 5.5 shows a striking difference in T2DM survival probability between ethnic groups, with South Asian participants having the highest probability of developing diabetes, followed by black participants. White participants had the highest survival probability from all ethnic groups, indicating that they are the ethnic group least affected from this disease in the WII study.

5.6 Crude and stratified prevalence and incidence rates of T2DM

Table 5.4 shows prevalence of T2DM in the WII study at each phase of data collection (phases 1-7).

Table 5.4 Prevalence of type 2 diabetes at clinical examination phases in the Whitehall II study

Screening phase	MEN	WOMEN
	% (N)	%(N)
phase 1 (1985-88)	0.7 (69)	0.7 (31)
phase 3 (1991-93)	2.3 (132)	2.3 (59)
phase 5 (1997-99)	4.4 (251)	4.7 (121)
phase 7 (2002-04)	7.2 (414)	8.4 (216)

Prevalence of T2DM among men rose from 0.7% in 1985-1988 to 2.3% in 1991-1993 to 4.4% in 1997-1999 to 7.2% in 2002-2004. Among women prevalence rose from 0.7% in 1985-1988 to 2.3% in 1991-1993 to 4.7% in 1997-1999 to 8.4% in 2002-2004. In the period 1991-1993, compared to the general England population, T2DM prevalence was slightly lower in the WII cohort among men and slightly higher among women (2.9% and 1.9% for men and women respectively in the 1994 Health Survey for England). As the WII cohort aged however, T2DM prevalence increased steeply and comparisons with the general population based on the Health Survey for England are not informative as the specific survey uses different cohorts of participants with the same age-range in each wave of screening.

The overall rate and 95% confidence intervals for the incidence of T2DM in the participants eligible for analysis, based on 922 incident T2DM cases, was 2.15 per 1000 person-years (95% CI: 2.02; 2.30) after a total of 428 053 person-years at risk. The incidence rate in the current sample of middle-aged white-collar men and women is similar to previous studies showing an incidence rate of 2.00-3.00 in Western European countries. Stratified incidence rates were calculated for selected sociodemographic characteristics, namely gender, age, employment grade and ethnicity (table 5.5).

Table 5.5 incidence rates of type 2 diabetes by study baseline (1985-88) sociodemographic factors after a 21 year follow-up of in the Whitehall II study

	T2DM cases	Person-years at risk	Rate (per 1000 p-y)	95% CI
Men	555	270 767	2.05	1.89 – 2.23
Women	276	118 005	2.34	2.09 – 2.63
Age-group				
35-39 years	191	122 326	1.56	1.35 – 1.80
40-44 years	185	114 522	1.61	1.40 – 1.87
45-49 years	216	85 590	2.52	2.21 – 2.88
50-55 years	330	105 615	3.12	2.81 – 3.48
Employment grade				
High	204	137 549	1.48	1.29 – 1.70
Middle	463	210 302	2.20	2.01 – 2.41
Low	255	80 202	3.18	2.81 – 3.59
Ethnic group				
European white	775	400 831	1.93	1.80 – 2.07
S.Asian	87	13 609	6.39	5.18 – 7.89
Black	43	8 914	4.82	3.58 – 6.50
Other	17	4 648	3.66	2.27 – 5.88

Table 5.5 shows incidence rates of T2DM by sociodemographic characteristics. These rates resemble the results presented for survival probabilities in figures 5.2-5.5. Women had a higher incidence rate than men. The incidence rate increased in a graded fashion from 1.56 in the youngest age group to 3.12 in the oldest age group. Incidence rates increased from 1.48 in the high employment grade to 2.20 in the middle employment grade to 3.18 in the low employment grade. The incidence rate of T2DM was substantially high among South Asians (6.39), who had more than 3 times the rate of white participants (1.93). Black participants were in-between with an incidence rate of 4.82, which was still more than twice the white rate.

5.7 Change in incidence rate of T2DM over time

Studies that investigated the hypothesized increase in T2DM rates over time found mixed results, with some studies showing an increase in rate and some no change. In the current analysis the change in incidence rates over the 21-year follow-up was calculated and is presented in tables 5.6 and 5.7 and figures 5.6 and 5.7.

Table 5.6 Yearly incidence rates for type 2 diabetes during a 21 year follow-up in the Whitehall II study

Time interval (years)	Participants at risk	T2DM cases	incidence rate
0-1	9527	3	0.31
1-2	9524	24	2.52
2-3	9465	10	1.06
3-4	9294	12	1.29
4-5	9183	82	8.93
5-6	8962	72	8.03
6-7	8786	65	7.40
7-8	8652	27	3.12
8-9	8400	15	1.79
9-10	8168	30	3.67
10-11	7943	73	9.19
11-12	7772	93	11.97
12-13	7580	28	3.69
13-14	7507	22	2.93
14-15	7302	39	5.34
15-16	7089	77	10.86
16-17	6918	118	17.06
17-18	6605	81	12.26
18-19	6430	41	6.38
19-20	4222	10	2.37
20-21	1759	0	0.00
21-22	25	0	0.00

Table 5.6 shows the incidence rate for T2DM for each consecutive year during follow-up. As already observed with survival probabilities (table 5.2), more T2DM cases were identified at clinical ascertainment phases, resulting in higher incidence rates of T2DM in the periods 4-7 years, 10-12 years and 15-18 years (table 5.7). Figure 5.6 shows graphically the 3 peaks in T2DM incidence over the 21 years of follow-up.

Figure 5.6 Yearly incidence rates for type 2 diabetes during a 21 year follow-up in the Whitehall II study

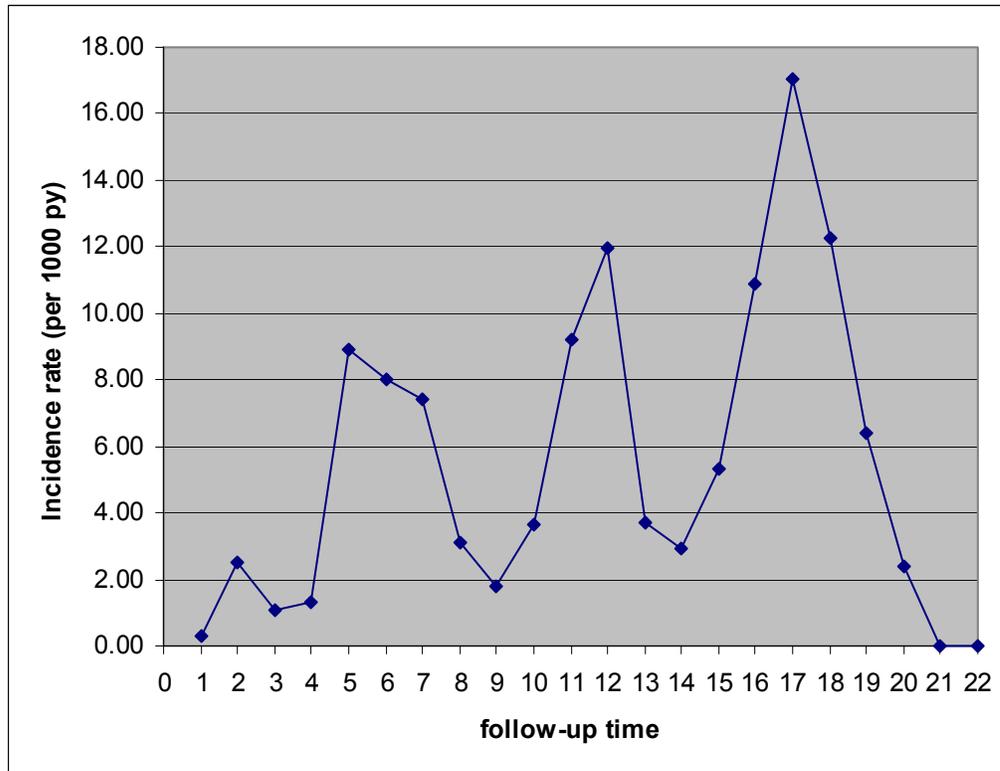


Figure 5.6 graphically displays the yearly incidence of T2DM during follow-up in the WII study. Prevalent diabetes cases at study baseline were excluded from this analysis. From this figure it can be seen that there is a pattern of increasing incidence through the years highlighted by the increasingly higher peaks observed at 5 years, 12 years and 17 years, which represent the cases ascertained from the clinical assessment of T2DM at phases 3, 5 and 7.

To further investigate the trend in incidence rate, follow-up time was split into three 7-year periods and the overall, as well as the yearly average for each period, incidence rate was calculated (table 5.7 and figure 5.7).

Table 5.7 Incidence rates of type 2 diabetes at 3 consecutive time periods during a 21 year follow-up in the Whitehall II study

Time interval (years)	Participants at risk	T2DM cases	Incidence rate (per 1000 person-years)	Average yearly incidence rate (per 1000 py)
0-7	9527	268	28.13	4.02
7-14	8652	288	33.29	4.76
14-21	7302	366	50.12	7.16

Figure 5.7 Average yearly incidence rates for type 2 diabetes at 3 consecutive time periods during a 21 year follow-up in the Whitehall II study

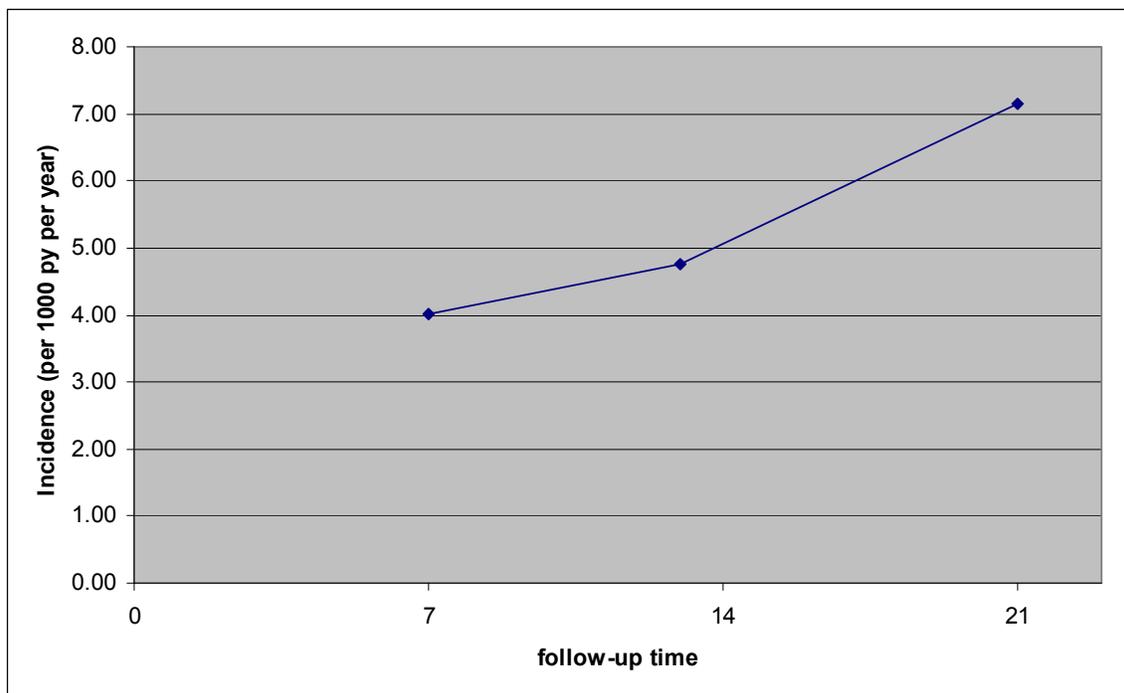


Table 5.7 and figure 5.7 shows the average yearly T2DM incidence rate during each 7-year period and confirm that T2DM incidence rates increased linearly from the period 0-7 years, to the period 7-14 years, to the period 14-21 years.

Average yearly incidence rates for T2DM were also calculated for different baseline age-groups in order to investigate whether the increase in rates applied to all age-groups (table 5.8 and figure 5.8).

Table 5.8 Incidence rates of type 2 diabetes at 3 consecutive time periods by age-group during a 21 year follow-up in the Whitehall II study

Time interval (years)	Participants at risk	T2DM cases	Overall incidence rate (per 1000 py)	Average yearly incidence rate (per 1000 py)
		<i>35-39 age group</i>		
0-7	2625	46	17.52	2.50
7-14	2451	64	26.11	3.73
14-21	2125	81	38.12	5.45
		<i>40-44 age group</i>		
0-7	2471	47	19.02	2.72
7-14	2293	56	24.42	3.49
14-21	2006	82	40.88	5.84
		<i>45-49 age group</i>		
0-7	1936	71	36.67	5.24
7-14	1728	59	34.14	4.88
14-21	1449	86	59.35	8.48
		<i>50-55 age group</i>		
0-7	2495	104	41.68	5.95
7-14	2180	109	50.00	7.14
14-21	1722	117	67.94	9.71

Figure 5.8 Average yearly incidence rates for type 2 diabetes at 3 consecutive time periods during a 21 year follow-up in the Whitehall II study by age group

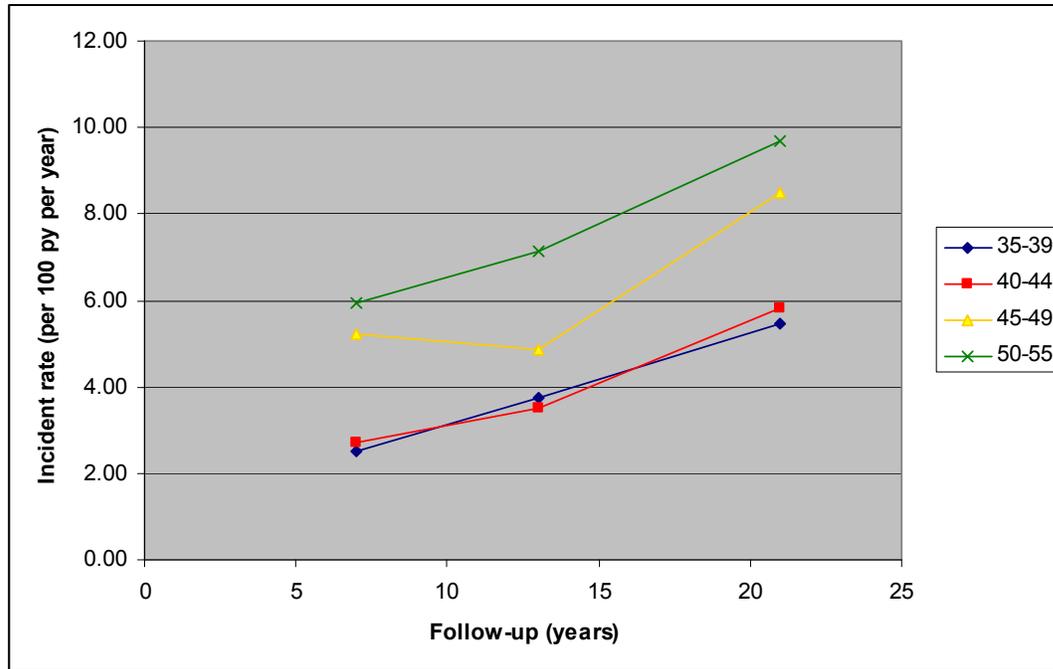


Table 5.8 and figure 5.8 indicate that T2DM incidence rates increased in all age-groups, confirming that the increase in rates spanned across all ages in the current sample.

In order to investigate whether the observed increase in T2DM rate (figures 5.7 and 5.8) was due to ageing of the cohort (cohort effect) or whether there was a secular increase in rate (period effect), table 5.9 was constructed.

Table 5.9 Incidence rates of type 2 diabetes by age and follow-up time during a 21 year follow-up in the Whitehall II study

Follow-up time (year intervals)	Age group						
	35-39	40-44	45-49	50-55	56-60	61-65	66-70
0-5	8.38	11.74	19.63	16.83	-	-	-
5-10	-	17.11	16.17	23.88	36.99	-	-
10-15	-	-	23.41	20.07	37.18	51.26	-
15-21	-	-	-	27.46	31.17	43.91	50.17

Table 5.9 shows T2DM rates over five year intervals of follow-up by age-group. The columns show rates for different sub-cohorts of participants over time belonging to the same age group. For example, the rate in the 40-44 year age-group was lower during the first 5 years of follow-up compared to the second 5 years. There is an increase in T2DM rate over time in the age-groups younger than 55 years and a decrease in rate in age-groups over 56 years. Overall, it could be said that the observed increase in T2DM incidence rate was not entirely due to the ageing of the cohort but this increase is not apparent at older ages.

5.8 Summary and link to next chapter

This chapter investigated crude and stratified incidence rates of T2DM and the change in incidence over time in the Whitehall II study over the period 1985-88 to 2002-2004. Based on the specific objectives, the current chapter identified that:

1. The crude T2DM incidence rate over the 21 year follow-up period of around 2 cases per 1000 person-years at risk was similar to previous studies in the UK and other western European countries. The probability of developing T2DM increased linearly with age, decreased linearly with employment grade and was lower in the white ethnic group compared to non-white ethnic minorities.
2. The crude prevalence and incidence rate of T2DM increased during follow-up. The increase in incidence over time was not attributed to the ageing of the cohort and was only apparent in younger ages, resulting in a decrease in rate in older ages.

The overall picture from the survival analysis is that incidence of T2DM is increasing among younger participants in the WII study and the disease is socially patterned. This is the only chapter in which analysis is conducted from study baseline (phase 1). The next results chapter (chapter 6) examines the association between sociodemographic, psychosocial, psychological, behavioural and biological factors and incident T2DM using

phase 3 to phase 7 as the follow-up time (see methods chapter, sub-section 4.1.1.5). Identifying determinants and risk factors for T2DM will help determine potential confounders and mediators in the psychosocial work stressors-incident T2DM association.

Chapter 6: Determinants and risk factors of type 2 diabetes in the Whitehall II study (1993-2004)

6.1 Introduction

The literature review in chapter 2 showed that there is strong evidence that health behaviours, obesity, cardiometabolic factors and inflammatory markers are associated with T2DM risk. There was also some evidence, though inconsistent, that these factors were associated with psychosocial work stressors, so they could act as potential mediators in the work stressors-incident T2DM association. In addition, socioeconomic factors, as well as psychosocial factors outside the workplace and psychological traits, could confound the association between work stressors and incident T2DM. However, before attempting to adjust for such potential confounders and mediators in the main analysis, it is essential to identify their association with incident T2DM in the current sample of WII participants.

In chronic disease epidemiology, the attribution of causation based on observational evidence is not straightforward. Determinants of chronic diseases such as CVD and T2DM are multiple, usually coexisting, risk factors which span from social to psychological to behavioural to biological. As described in the thesis introduction chapter, the term determinant is used to describe sociodemographic factors that are linked to the development of disease. A risk factor is any factor that plays an essential role in producing an occurrence of the outcome (Last, 2001). A risk marker is any factor that is associated with risk of disease but whose *causal* contribution to the development of the specific disease is questionable, either due to inconsistent findings in the literature and/or a lack of biological plausibility for the association.

Many factors have been implicated in the development of T2DM, spanning all layers of the causal web (Krieger, 1994). These include socioeconomic (i.e. low occupational class, low educational attainment) (Sporston & Primatesta, 2003; Connolly et al, 2000;

Evans et al, 2000), psychosocial (i.e. life events and social isolation) (Mooy et al, 2000; Robinson & Fuller, 1985; Strodl & Kenardy, 2006, 2008; Raikkonen et al, 2007; Chida & Hammer), psychological (i.e. anger and hostility) (Golden et al, 2006), behavioural (i.e. poor diet, inactivity) (Roumen et al, 2009), cardiometabolic (i.e. obesity, insulin resistance, adverse lipid profile and hypertension) (Rader et al, 2007) and inflammatory (i.e. fibrinogen and CRP) (Pickup, 2004). In a rigorous review of conventional and novel risk factors for T2DM it was concluded that due to methodological limitations, such as colinearity of risk factors, residual confounding and overadjustment all the specific risk factors for T2DM are not yet established (Sattar et al, 2008).

This chapter is divided into: (i) identification of factors associated with incident T2DM, which *do not* lie in the causal pathway between work stressors and T2DM (potential confounders); and (ii) identification of factors associated with incident T2DM, which *do* lie in the causal pathway between work stressors and T2DM (potential mediators).

6.2 Chapter aim, objectives and main hypotheses

Aim:

To identify potential confounders or mediators in the association between psychosocial work stressors and type 2 diabetes.

Objectives:

1. To assess age-adjusted and multivariate adjusted associations between socioeconomic, psychosocial, psychological, behavioural and biological factors and incident T2DM.
2. To compare the predictive power of BMI to measures of central obesity in determining incident T2DM cases and choose the most suitable variable for further analysis.

3. To use multivariate regression techniques for examining the statistical independence of the association between correlated biological factors and incident T2DM.

Hypotheses:

1. Socioeconomic, psychosocial, psychological, behavioural and biological factors are associated with incident T2DM in age-adjusted analysis in the Whitehall II study.
2. Central obesity measures are better than BMI in predicting incident T2DM cases.

6.3 Chapter methodology

6.3.1 Sample description

As discussed in the methods chapter (sub-section 4.4.2, figure 4.15), the baseline for the main analysis, including the current chapter was phase 3. Ethnic minority participants were excluded from the analysis (n=532), as were participants who had missing data on all psychosocial work stressors (n=1329). Finally, those identified as prevalent diabetes cases up to phase 3 were excluded (n=1052). The final number of participants included in the analysis was 5895 (4166 men, 1729 women). This is the specific sample on which further analysis will be conducted.

6.3.2 Variables used in current chapter

The variables used in the current chapter, together with the sub-section in which they were described in the methods section, are listed below:

- Incident T2DM (4.2.2.1)
- Age (4.2.2.3.2)
- Employment grade (4.2.2.3.2)
- Educational attainment (4.2.2.3.3)

- Father's social class (4.2.2.3.4)
- Life satisfaction (4.2.2.4.1)
- Life events (4.2.2.4.2)
- Isolation (4.2.2.4.3)
- Anger (4.2.2.4.4)
- Hostility (4.2.2.4.5)
- Affect balance (4.2.2.4.6)
- Type A personality (4.2.2.4.7)
- Chronic general psychological wellbeing (4.2.2.4.8)
- Dietary energy density (4.2.2.5.1.2)
- Wholegrain cereal consumption (4.2.2.5.1.3)
- Dietary patterns (4.2.2.5.1.4)
- Energy Intake:Total Energy Expenditure (4.2.2.5.1.5)
- Physical activity (4.2.2.5.2)
- Alcohol consumption (4.2.2.5.3)
- Smoking status (4.2.2.5.4)
- Height (4.2.2.6.1.1)
- Body Mass Index (4.2.2.6.1.1)
- Waist circumference (4.2.2.6.1.2)
- Waist-hip ratio (4.2.2.6.1.2)
- Waist-height ratio (4.2.2.6.1.2)
- Triglycerides (4.2.2.6.1)
- HDL cholesterol (4.2.2.6.1)
- Systolic blood pressure (4.2.2.6.2)
- Fibrinogen (4.2.2.6.3.1)
- C-reactive protein (4.2.2.6.3.2)
- Interleukin-6 (4.2.2.6.3.3)
- von Willebrand factor (4.2.2.6.3.4)
- Factor VII (4.2.2.6.3.5)
- Menopausal status (4.2.2.6.4.1)

- Hormone replacement therapy (4.2.2.6.4.1)
- Contraceptive pill use (4.2.2.6.4.2)

6.3.3 Statistical analysis

The distribution of the exposure variables to be tested in relation to incidence of T2DM among the Whitehall II participants is displayed in table 6.1. A chi-squared test was used to assess gender differences in prevalence for categorical variables, while a t-test is used to assess gender differences in mean for continuous variables.

The main analysis of the chapter was carried out using Cox proportional regression models. A detailed description of Cox proportional hazards regression can be found in methods chapter, section 4.4.2. Briefly, Cox regression calculates rate ratios (which are more usually referred to as hazard ratios in survival analysis) as exponentiated coefficients comparing the incidence rates between the categories of an exposure variable (men vs. women; different age-groups; etc.). The proportional hazards assumption (see methods chapter) was met for all exposure variables. The hazard ratios presented in the tables represent relative risks for T2DM for each category of exposure (if the exposure variable is categorical) or the increase in the risk of T2DM per 1 standard deviation increase in exposure (if the exposure variable is continuous). The follow-up for incident T2DM was from phase 3 (1991-93) to phase 7 (2002-04). The maximum follow-up time was 14.7 years.

6.3.3.1 Age-adjusted analysis

The association of each exposure variable with incident T2DM was assessed separately in age-adjusted Cox proportional hazards regression analysis. For example:

$$h(t) = h_0(t) * \exp(\beta_1 age + \beta_2 employment\ grade)$$

$$h(t) = h_0(t) * \exp(\beta_1 age + \beta_2 educational\ attainment)$$

etc.

For continuous variables, the likelihood ratio test was used to test whether the quadratic and cubic terms significantly improved the model containing the linear term of the variable (methods chapter, sub-section 4.3.3.6). For example:

$$h(t) = h_0(t) * \exp(\beta_1 age + \beta_2 dietary\ energy\ density)$$

estimates store a

$$h(t) = h_0(t) * \exp(\beta_1 age + \beta_2 dietary\ energy\ density^2)$$

estimates store b

lrtest a b

The hazard ratios presented in the tables represent relative risks for T2DM for each category of exposure (categorical exposures), or the increase in the risk of T2DM per 1 standard deviation increase in risk of the exposure (continuous exposures). P-values of <0.05 were taken as evidence for an association.

6.3.3.2 Multivariate adjusted analysis

The principles of multivariate adjusted Cox regression analysis are the same as age-adjusted analysis. Briefly, including several variables simultaneously in a multivariate adjusted model in multivariate adjusted Cox regression analysis results in mutual adjustment for all variables (i.e. each variable included is adjusted for the rest of the variables in the model). For example:

$$h(t) = h_0(t) * \exp(\beta_1 age + \beta_2 blood\ pressure + \beta_3 triglycerides + \beta_4 HDL + \dots + \beta_n x_n)$$

6.3.3.3 Analysis for comparing predictability of related variables and for identification of statistically independent associations

After investigating associations between all exposure variables and incident T2DM in age-adjusted analysis, biological factors were further analyzed in order to disentangle the effects of different associated variables. For the other categories of factors, namely socioeconomic, psychosocial, psychological and behavioural, further analysis was not

needed as associations with incident T2DM were limited to only a few variables and the issue of colinearity was not a problem among those.

Biological risk factors were further divided into 4 sub-categories: (i) anthropometric factors (height, BMI, waist circumference, WHR and waist-height ratio); (ii) cardiometabolic factors (systolic blood pressure, plasma triglycerides and HDL cholesterol); (iii) inflammatory factors (fibrinogen, CRP, IL-6, von Willebrand factor and factor VII); and (iv) reproductive factors (menopausal status, hormone replacement therapy use and oral contraceptive pill use).

ROC analysis was used for comparing the predictive power of 3 central obesity measures (waist circumference; waist-hip ratio; and waist-height ratio) to BMI in determining incident T2DM cases during follow-up. ROC analysis was described in the methods chapter, section 4.3.5. Briefly, ROC analysis can test the overall ability of continuous measures to discriminate between diseased and non-diseased individuals by producing ROC curves of sensitivity v. 1-specificity. The area under the ROC curve (AUC) provides an estimate of the predictive power of a variable or model in identifying disease cases. An AUC of 1 means perfect prediction. An AUC of 0.5 means zero prediction

Backwards modelling was performed for investigating the effect of subsequent removal of a variable (or variables) from a maximally adjusted model containing all assessed biological variables. A likelihood ratio test was performed each time a variable was removed to assess the effect of removal of the specific variable(s) on the overall maximum likelihood of the model (methods chapter, sub-section 4.4.3.6.2). A statistically significant LRT p-value, indicates that the removed variable significantly improved the model. In other words, evidence that the variable was (statistically) independently associated with incident T2DM.

6.4 Factors associated with incident T2DM in the Whitehall II study

This section presents results on the effect of potential confounders (socioeconomic, psychosocial, psychological, and reproductive) and mediators (behavioural,

anthropometric, cardiometabolic and inflammatory) on risk of T2DM. Comparison to results from other studies follows evidence from the current results.

6.4.1 Distribution of factors by gender (Table 6.1)

Table 6.1 shows the distribution of potential risk factors for T2DM among men and women cross-sectionally at phase 3 of the WII study. Categorical variables are presented as prevalence, while continuous variables as mean with its standard error.

Table 6.1 Distribution of sociodemographic, behavioural and biological characteristics among men and women selected for analysis at WII phase 3

	MEN		WOMEN		<i>p for gender difference</i>
	N	mean (s.e)	N	mean (s.e)	
Age	4166	48.6 (0.09)	1729	49.8 (0.14)	<0.001
Employment grade %					
High	2620	51.0	355	16.9	
Middle	2225	43.3	982	46.6	
Low	295	5.7	770	36.5	<0.001
Educational attainment %					
University degree	1602	38.9	374	25.5	
Secondary education	2255	54.8	727	49.6	
No formal education	258	6.3	366	24.9	<0.001
Father's social class%					
Non-manual (I, II, IIINM)	2849	59.7	916	48.0	
IIIM	1362	28.5	646	33.8	
IV+V	565	11.8	347	18.2	<0.001
Life satisfaction (score)	3107	15.7 (0.13)	1280	15.7 (0.20)	0.96
Upset by life events (score)	4082	2.52 (0.04)	1654	3.57 (0.08)	<0.001
Isolation (score)	4108	2.01 (0.02)	1692	2.29 (0.03)	<0.001
Anger (score)	1325	6.37 (0.11)	614	7.07 (0.16)	<0.001
Hostility (score)	2816	10.8 (0.11)	1097	10.3 (0.17)	0.011
Affect balance(score)	3064	3.71 (0.7)	1239	3.10 (0.13)	<0.001
Type A personality (score)	4072	13.4 (0.10)	1659	13.1 (0.16)	0.14
Chronic GHQ (score)	4163	8.64 (0.10)	1727	9.59 (0.15)	<0.001
Alcohol consumption (units/week) %					
no	683	13.3	574	27.3	
moderate	3852	74.9	1449	68.8	
heavy	607	11.8	82	3.9	<0.001

Smoking status %					
never	2422	48.0	1061	52.0	
ex	2005	39.7	615	30.1	
current	621	12.3	366	17.9	<0.001
Dietary pattern %					
healthy	1395	30.0	768	42.2	
Mediterranean-like	866	18.6	351	19.3	
sweet	814	17.5	113	6.2	
unhealthy	1575	33.9	589	32.3	<0.001
Dietary energy density (kcal/g)	4134	1.18 (0.01)	1714	1.03 (0.01)	<0.001
Wholegrain cereal (g/week)	4166	127.5 (1.51)	1729	112.9 (2.18)	<0.001
Physical activity (MET-hrs/d)	4166	3.7 (0.01)	1729	3.1 (0.01)	<0.001
Height (cm)	4157	176.8 (0.10)	1727	162.3 (0.15)	<0.001
BMI (kg/m²)	4153	25.1 (0.05)	1726	25.4 (0.11)	0.002
Waist circumference (cm)	4098	89.3 (0.15)	1717	77.1 (0.29)	<0.001
Waist-hip-ratio	4094	0.94 (0.02)	1716	0.79 (0.01)	<0.001
Waist-height ratio	4092	0.51 (0.01)	1716	0.48 (0.01)	<0.001
Systolic blood pressure (mmHg)	4152	121.6 (0.20)	1728	117.2 (0.32)	<0.001
Triglycerides (mmol/L)	4139	1.57 (0.02)	1712	1.17 (0.02)	<0.001
HDL-cholesterol (mmol/L)	4124	1.32 (0.01)	1712	1.69 (0.01)	<0.001
Fibrinogen (g/l)	3859	2.32 (0.01)	1630	2.56 (0.01)	<0.001
C-reactive protein (mg/l)	3953	1.74 (0.06)	1629	2.10 (0.10)	<0.001
Interleukin-6 (ng/l)	3895	1.78 (0.04)	1645	2.17 (0.06)	<0.001
von Willebrand factor (IU/ml)	3758	106.4 (0.65)	1562	107.1 (1.00)	0.53
factor VII (IU/ml)	3870	89.4 (0.47)	1614	93.4 (0.74)	<0.001
Menopause %	n/a	n/a	847	49.0	n/a
Hormone replacement therapy %	n/a	n/a	399	23.1	n/a
Contraceptive pill use %	n/a	n/a	907	55.2	n/a

Men were slightly younger than women. Compared to women, men were more likely to be in the higher employment grade, to have university education qualifications and to come from a higher father's social class. Men reported less isolation, anger, hostility and being upset by life events. Furthermore men's affect balance leaned more towards a positive affect state and were better in terms of psychological wellbeing as indicated by the lower GHQ score. Men consumed larger absolute amounts of wholegrain cereals and were more likely to be moderate drinkers, less likely to be current smokers and were

more physically active. Men had a lower BMI and lower levels of all the inflammatory markers.

Women on the other hand, were more likely to have an overall healthy dietary pattern, and had a lower dietary energy density. Compared to men, women had lower levels central obesity measured by waist circumference, WHR and waist-height ratio, lower systolic blood pressure, lower triglyceride levels and higher HDL cholesterol. Almost half of the women were post-menopausal and 1 in 4 was on hormone replacement therapy currently or in the past. More than half of women used oral contraceptive pills.

In general, in the current sample, men are socially and psychosocially advantaged and have a better psychological state. Men also have a healthier lifestyle (apart from dietary intake) and body weight (as measured by BMI), as well as lower activation of innate immunity. Women in the current sample are clearly socially disadvantaged compared to men, which is probably reflected in their worse psychological state. Despite their rather unhealthier lifestyle (apart from dietary patterns) women have a much healthier cardiometabolic risk profile, with lower levels of central obesity, blood pressure and triglycerides and higher HDL-cholesterol.

The overall rate and 95% confidence intervals for the incidence of T2DM in the participants eligible for analysis was 4.82 per 1000 person-years (95% CI: 4.31; 5.39) after a total of 68 930 person-years at risk.

6.4.2 Potential confounding factors and risk of T2DM (Tables 6.2-6.4)

6.4.2.1 Sociodemographic factors and risk of T2DM (Table 6.2)

Table 6.2 presents the effect of gender and age on risk of T2DM, as well as age-adjusted estimates for the effect of socioeconomic factors. Three indicators of SEP were assessed in the current analysis: civil service employment grade, educational attainment and father's social class.

Table 6.2 Age-adjusted Hazard Ratios (95% Confidence Intervals) for the effect of sociodemographic characteristics on incident type 2 diabetes among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	<i>No of cases/total</i>	Hazard Ratios (95% CI)	<i>No of cases/total</i>	Hazard Ratios (95% CI)
Age group				
39-44	49/1248	reference	17/422	reference
45-49	60/1258	1.24 (0.85; 1.81)	15/456	0.82 (0.41; 1.64)
50-54	41/822	1.33 (0.88; 2.01)	23/373	1.71 (0.91; 3.20)
55-63	66/838	2.20 (1.52; 3.17)	37/478	2.42 (1.36; 4.30)
<i>trend p-value</i>		<0.001		<0.001
Employment grade				
High	97/2108	reference	7/312	reference
Middle	104/1825	1.43 (1.08; 1.89)	51/819	2.82 (1.28; 6.22)
Low	14/229	1.89 (1.08; 3.30)	34/598	2.58 (1.12; 5.93)
<i>trend p-value</i>		0.002		0.082
Educational attainment				
University degree	67/1364	reference	8/343	reference
Secondary education	114/1853	1.23 (0.95; 1.66)	43/628	2.73 (1.27; 5.87)
No formal education	9/198	0.85 (0.42; 1.70)	21/288	2.50 (1.07; 5.86)
<i>trend p-value</i>		0.55		0.063
Father's social class				
Non-manual (I, II, IIINM)	118/2337	reference	44/769	reference
IIIM	59/1080	1.08 (0.79; 1.47)	20/524	0.61 (0.36; 1.03)
IV+V	33/479	1.35 (0.91; 1.98)	20/282	1.06 (0.62; 1.81)
<i>trend p-value</i>		0.16		0.81

Decreasing employment grade was associated with an increased risk of T2DM and the effect was stronger in women (2.5~fold increased risk comparing lowest to highest grade) than men (2~fold increased risk). The statistical test for interaction for gender differences was not significant however. In women despite the increased risk of T2DM in the middle and low grades, there was weak evidence for a linear associated with decreasing employment grade (p for trend=0.082).

Decreasing educational attainment was associated with a higher risk of T2DM in women but not in men (p for gender interaction=0.052). In the unadjusted analysis, women with

no formal educational had 2.5~fold increased risk of T2DM compared to women with a university degree. Like employment grade, decreasing educational attainment was not linearly associated with increasing risk (p for trend=0.063). Father's social class was not associated with T2DM risk in either men or women.

These findings are in agreement with a previous analysis in the WII study looking at risk factors for T2DM during a different follow-up (phases 1-5) (Kumari et al, 2004). The authors of that paper found a 3-fold higher risk for T2DM in men in the lower compared to the higher grade and a 70% higher risk in women, but the effect of educational attainment and father's social class was not assessed. Educational attainment was associated with the metabolic syndrome (a major risk factor of T2DM) among a representative sample of British men and women (Langenberg et al, 2006).

Studies from around the world show clearly that there is a consistent association between SEP and T2DM. An inverse association between SEP and T2DM was found, among other countries, in England (Connolly et al, 2000; Sporston & Primatesta, 2003; Kumari et al, 2004), Scotland (Evans et al, 2000) Sweden (Agardh et al, 2004; Agardh et al, 2007) Germany (Icks et al, 2007), France (Dalichampt et al, 2008), Spain (Larrañaga et al, 2005), the US (Robbins et al, 2005; Wilder et al, 2005; Wray et al, 2006; Lidfeldt et al, 2007), Canada (Yu & Raphael, 2004; Rabi et al, 2006), Japan (Toshihiro et al, 2008) and among Filipino-American women (Langenberg et al, 2007). Detailed investigation of this social inequality in T2DM is beyond the scope of the current project.

6.4.2.2 Psychosocial and psychological factors and risk of T2DM (Table 6.3)

For the current project, the term psychosocial is used to describe characteristics or situations where the psychology of people is affected by some condition related, at some extent, to society and to interactions between people within a society. Based on this, life satisfaction, upset by life events, isolation, anger and hostility are considered psychosocial characteristics. The term psychological is used to describe psychological states that have to do more with the person as an individual rather than his/her interaction

with society. Based on this, affect balance, type A personality and general psychological wellbeing are considered as psychological characteristics. Associations between psychosocial and psychological factors and incident T2DM is presented in table 6.3.

Table 6.3 Age-adjusted Hazard Ratios (95% Confidence Intervals) for incident type 2 diabetes per 1 s.dev increase in psychosocial and psychological characteristics among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	Hazard Ratios (95% CI)	<i>p-value</i>	Hazard Ratios (95% CI)	<i>p-value</i>
Life satisfaction	0.95 (0.81; 1.12)	<i>0.56</i>	0.81 (0.64; 1.02)	<i>0.08</i>
Upset by life events	1.24 (1.08; 1.43)	<i>0.003</i>	1.08 (0.90; 1.31)	<i>0.41</i>
Isolation	0.95 (0.83; 1.10)	<i>0.52</i>	0.95 (0.77; 1.18)	<i>0.65</i>
Anger	1.09 (0.87; 1.38)	<i>0.45</i>	0.90 (0.62; 1.30)	<i>0.57</i>
Hostility	1.12 (0.95; 1.33)	<i>0.19</i>	0.94 (0.70; 1.25)	<i>0.65</i>
Affect balance	1.02 (0.86; 1.21)	<i>0.81</i>	0.84 (0.67; 1.05)	<i>0.13</i>
Type A personality	0.99 (0.86; 1.13)	<i>0.88</i>	1.00 (0.81; 1.25)	<i>0.98</i>
Chronic GHQ	0.96 (0.83; 1.10)	<i>0.57</i>	0.99 (0.80; 1.22)	<i>0.91</i>

Table 6.3 shows that in this specific sample of the WII study, psychosocial and psychological characteristics were not associated with incident T2DM, with the exception of life events. The more upset participants reported being by life events the higher was the risk of T2DM. Every increase in 1 standard deviation in the upset by life events score was associated with a 24% higher risk of T2DM among men. This supports previous evidence on the harmful role of adverse life events in the development of T2DM. The effect of psychosocial and psychological factors on incident T2DM may be underestimated in the current analysis, as these factors were assessed at phase 1 (apart from chronic GHQ) At phase 3, however, prevalent T2DM cases were excluded from analysis and thus the effect of phase 1 psychosocial and psychological characteristics from phase 3 onwards may be diluted by selection bias.

Evidence on the role of psychosocial factors and the aetiology of T2DM is scarce and inconsistent in the literature, apart from consistent evidence on the harmful role of

adverse life events (Grant et al, 1974; Robinson & Fuller, 1985; Mooy et al, 2000; Raikkonen et al, 2007). In addition, evidence from a large Australian survey comprising of more than 10 000 elderly women revealed that not living with a partner and having an adverse mental health index was associated with newly diagnosed T2DM (Strodi & Kenardy, 2006). Anger was associated with increased risk of T2DM in the ARIC study (Golden et al, 2006). In studies investigating the association between psychosocial factors and heart disease, it was found that social isolation (Chesney et al, 1993; Orthomer et al, 1998a,b), hostility (Grothe et al, 2008; Everson-Rose et al, 2006; Niaura et al, 2002), type A personality (Myrtek, 2001) and psychological distress as, assessed by the GHQ, (Rasul et al, 2005) predicted incidence of heart disease. Hostility, anger and isolation were found to be associated with triglycerides, HDL and blood pressure (Keltikangas-Jarvinen & Ravaja, 2002). In the WII study negative affect, but not affect balance, was associated with incident coronary heart disease (Nabi et al, 2008).

6.4.2.3 Reproductive factors among women (Table 6.4)

There is some evidence in the literature that reproductive factors are associated with T2DM risk in women. Table 6.4 shows the effect of menopausal status, hormone replacement therapy and oral contraceptive pills on risk of T2DM among women.

Table 6.4 Age-adjusted Hazard Ratios (95% Confidence Intervals) for the effect of reproductive characteristics on incident type 2 diabetes among women after 15 years of follow-up in the Whitehall II study

	No of cases/total	Hazard Ratios (95% CI)
Post-menopause*	51/847	1.67 (0.91; 3.08)
Hormone replacement therapy use*	24/399	1.02 (0.63; 1.64)
Oral contraceptive use*	46/907	0.91 (0.59; 1.41)

* post-menopausal compared to pre-menopausal; use of hormone replacement therapy compared to no use; use of oral contraceptives compared to no use

Table 6.4 shows that, after adjusting for age, postmenopausal women had 67% higher risk of T2DM compared to pre-menopausal women. This effect did not reach statistical

significance however. Hormone replacement therapy and use of oral contraceptive medication were not associated with incident T2DM (table 6.4). Further investigation or discussion of these findings was not considered necessary.

In a large cross-sectional survey in Italy, post-menopausal status was associated with a higher prevalence of T2DM, while, in the same study, hormone replacement therapy was associated with a lower prevalence irrespective of age (Di Donato et al, 2005). In a Japanese nested case-control study, oral contraceptive use was associated with higher odds of T2DM but only among pre-menopausal women (Rosenthal et al, 2004). In another nested case-control study, plasma levels of the sex steroid hormone oestradiol were strongly associated with odds of T2DM among post-menopausal women. A synthetic form of oestradiol is a major component of oral contraceptive medication

6.4.3 Potential mediating factors and risk of T2DM (Tables 6.5-6.6 and 6.9-6.13)

6.4.3.1 Behavioural factors and risk of T2DM (Tables 6.5 and 6.6)

The age-adjusted association between health behaviours and incident T2DM is presented in table 6.5. Associations from multivariate analysis from a model containing all health behaviours associated with incident T2DM in the age-adjusted analysis are presented in table 6.6.

Table 6.5 Age-adjusted Hazard Ratios (95% Confidence Intervals) for the effect of behavioural factors on incident type 2 diabetes among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	No of cases/total	Hazard Ratios (95% CI)	No of cases/total	Hazard Ratios (95% CI)
Physical activity (MET-hrs/d)		0.78 (0.64; 0.94)		0.92 (0.72; 1.18)
Dietary energy density (kcal/g)		0.95 (0.81; 1.11)		1.21 (0.98; 1.49)
Wholegrain cereal (g/week)*		0.81 (0.69; 0.94)		1.19 (0.98; 1.44)
Dietary pattern				
healthy	45/1154	reference	36/650	reference
Mediterranean-like	42/722	1.65 (1.07; 2.53)	13/298	0.83 (0.42; 1.62)
sweet	35/658	1.53 (0.96; 2.44)	6/99	1.09 (0.41; 2.86)
unhealthy	80/1272	1.73 (1.18; 2.53)	28/484	1.15 (0.67; 1.92)
<i>heterogeneity</i>		0.021		0.82
<i>p-value</i>				
Alcohol cons.(units/week)				
no	22/560	reference	34/453	reference
moderate	169/3097	1.18 (0.76; 1.84)	55/1207	0.58 (0.38; 0.89)
heavy	24/507	1.11 (0.62; 1.98)	3/69	0.62 (0.19; 2.01)
<i>heterogeneity</i>		0.63		0.010
<i>p-value</i>				
Smoking status				
never	96/2012	reference	47/901	reference
ex	78/1625	0.98 (0.73; 1.32)	31/490	1.13 (0.72; 1.78)
current	40/472	2.13 (1.47; 3.08)	14/296	0.97 (0.53; 1.77)
<i>heterogeneity</i>		0.001		0.69
<i>p-value</i>				

*HR per 1 s.dev increase in exposure for continuous variables

Table 6.5 shows age-adjusted associations between health behaviours and incident T2DM among men and women. Multivariate adjusted Cox regression analysis was used to disentangle the effects of the behavioural factors (table 6.6). The effect of behavioural factors on incident T2DM differed by gender in unadjusted analysis so separate analysis was used for men and women. Dietary patterns, physical activity and smoking were entered in the model in men. For women dietary energy density, physical activity and alcohol consumption were entered in the model.

Table 6.6 Adjusted* Hazard Ratios (95% Confidence Intervals) for the effect of behavioural factors on incident type 2 diabetes among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	No of cases/total	Hazard Ratios (95% CI)	No of cases/total	Hazard Ratios (95% CI)
Dietary energy density (kcal/g)**				1.22 (0.99; 1.50)
Diet cluster				
Healthy	44/1142	reference	n/a	n/a
Mediterranean-like	42/715	1.71 (1.11; 2.63)		
Sweet	34/642	1.50 (0.93; 2.41)		
Unhealthy	80/1256	1.54 (1.04; 2.27)		
<i>heterogeneity</i>		0.082		
<i>p-value</i>				
Physical activity (MET-hrs/d)				
T1	66/963	reference	42/672	reference
T2	72/1412	0.74 (0.53; 1.03)	31/603	0.88 (0.54; 1.45)
T3	62/1380	0.66 (0.47; 0.94)	19/439	0.69 (0.38; 1.34)
<i>trend</i>		0.023		0.22
<i>p-value</i>				
Alcohol consumption (g/week)				
No	n/a	n/a	34/449	reference
Moderate			55/1198	0.58 (0.37; 0.93)
Heavy			3/67	0.67 (0.20; 2.21)
<i>heterogeneity</i>				0.029
<i>p-value</i>				
Smoking status				
Never	87/1847	reference	n/a	n/a
Ex	75/1484	1.09 (0.74; 1.38)		
Current	38/424	2.00 (1.35; 2.96)		
<i>heterogeneity</i>		0.003		
<i>p-value</i>				

*mutually adjusted

**HR per 1 s.dev increase in exposure for continuous variables

6.4.3.1.1 Dietary intake

Three measures of dietary intake were included in the current analysis: (i) dietary patterns; (ii) dietary energy density; and (iii) wholegrain cereal consumption. In age-adjusted analysis (table 6.5), the effect of diet measures differed in men and women.

Consumption of wholegrain cereals had a protective effect on T2DM risk which was only apparent in men (p for gender interaction=0.10). Each increase in 1 standard deviation of wholegrain cereal consumption was associated with a 19% lower risk of T2DM. In men again, compared to participants in the healthy dietary pattern (reference category), participants in all other diet patterns (Mediterranean-like, sweet and unhealthy) had a higher risk for T2DM. This higher risk reached statistical significance for the Mediterranean-like (65% higher risk) and unhealthy diet (73% higher risk). Dietary energy density, a holistic measure of dietary intake characterizing a diet on the basis of the energy (kcal) it provides per gram of food, was associated with T2DM risk only among women. For each increase in 1 standard deviation increase in dietary energy density there was a 21% increase in the risk of T2DM in women. For dietary energy density there was evidence for departure from linearity among women. The quadratic effect (energy density²) improved the model containing only the linear term of energy density (LRT p=0.006) and thus both the linear and quadratic terms were entered in the model.

In adjusted analysis (table 6.6) the effect of dietary patterns on incident T2DM in men was altered, in that the risk associated with the unhealthy dietary pattern was reduced from 73% higher risk to 54% higher risk, while the effect associated with the Mediterranean-like pattern increased from 65% higher risk to 71% higher risk. Among women, the effect of dietary energy density remained robust to adjustment for physical activity and alcohol consumption.

It is widely accepted that in observational epidemiological studies investigation of diet-disease associations is very difficult if not problematic. The main issues underlining this phenomenon are (i) the misreporting of dietary intake, which introduces information bias in the results and (ii) residual confounding by socioeconomic factors and other health behaviours, which are associated with both dietary intake and disease risk. In the current analysis both issues were dealt with by adjusting for employment grade and for energy misreporting. Details for the adjustment for misreporting and the variables used can be found in the methods chapter.

The advantage of dietary pattern as the exposure measure is that it represents a more holistic assessment of diet rather than concentrating in a specific nutrient or food group (Brunner et al, 2008). The associations between diet and incident T2DM in the current analysis would have probably been even stronger if information bias due to misreporting (which is assumed to always exist at some degree in dietary assessment even after adjustment for misreporting) (Black, 2000) was not present.

Studies which have attempted to establish an association between diet and T2DM consistently found evidence for an association between wholegrain cereal consumption and T2DM risk and saturated fat intake and T2DM risk (van Dam, 2003). Consumption of saturated fat was shown to decrease insulin sensitivity irrespective of changes in body weight, with the mechanisms believed to involve alterations in fatty acid content of cell membranes resulting in impaired cell signalling. Low consumption of dietary fibre has been linked to higher post-prandial glucose and insulin response, unhealthier lipid profile and lower insulin sensitivity (Parillo & Riccardi 2004; Mann, 2002), which contribute to T2DM development.

Higher energy density diets are characterized by a higher consumption of fats and processed carbohydrates and lower consumption of wholegrain products, fruits and vegetables. Also, in the current project, the unhealthy diet pattern is characterized by higher than average consumption of meat, sausages, white bread, fries and full-cream milk; average consumption of wine and beer; and very low consumption of fruits and vegetables. The Mediterranean-like dietary pattern is characterized by higher than average consumption of wholegrain bread, fruits, vegetables, pasta, rice, wine and beer; low intake of full-cream milk but high intake of butter; and average consumption of white bread (Brunner et al, 2008). It can therefore be concluded that the current results are in agreement with previous evidence on the role of diet in the development of T2DM.

6.4.3.1.2 Physical activity

In the age-adjusted model (table 6.5) physical activity was linearly associated with a decreased risk of T2DM in men but not women. The test for gender interaction was not significant ($p=0.79$). In men, 1 standard deviation increase in physical activity was associated with 22% decrease in risk of T2DM. When an ordered categorical variable (tertiles of the continuous variable) was used, those in the highest physical activity tertile had a 32% lower risk of T2DM compared to the lowest tertile in women (result not shown), thus the physical activity variable was included in adjusted analysis for women as well.

In the adjusted model (table 6.6), an ordered categorical variable (physical activity tertiles) was used since this variable was more strongly linked to incident T2DM than the continuous variable in both men and women. Adjusting for other health behaviours (diet and smoking in men; diet and alcohol consumption in women) in the multivariate adjusted behavioural model did not attenuate the protective effect of physical activity on T2DM. The effect only reached statistical significance in men however. After controlling for the other health behaviours, men in the highest tertile of physical activity had a 34% lower risk of T2DM compared to men in the lowest tertile.

The literature on the protective effect of physical activity on T2DM risk is consistent. The importance of physical activity as a protective factor for type 2 diabetes is supported by a large body of evidence from epidemiological studies (Helmrich et al, 1991; Manson et al, 1991; Manson et al, 1992; Burchfiel, 1995; Lynch et al, 1996; Haapanen et al, 1997; Hu et al, 1999; Folsom et al, 2000; Hu et al, 2001; Meisinger et al, 2002; Gill & Cooper, 2008).

Physical activity is essential for maintaining the balance between energy intake and energy expenditure. Physical activity can therefore prevent weight gain and enhance weight loss. Physical activity can protect from the development of T2DM also through pathways other than maintaining energy balance and an ideal body weight/composition. Physical activity can improve insulin sensitivity by increasing insulin-stimulated

glycogen synthesis due to an increased rate of insulin-stimulated glucose transport/phosphorylation. Mechanisms involved in this extra protective effect of physical activity are increased activity of GLUT4 glucose transporters, an overall increase in skeletal muscle mass, an increase in the proportion of more insulin sensitive types of skeletal muscle fibres and skeletal muscle capillary proliferation (Perseghin et al, 1996; Goodyear et al, 1998). The stronger effect of physical activity in men may be due to the overall higher physical activity level of men compared to women.

6.4.3.1.3 Alcohol consumption

In the unadjusted model moderate alcohol consumption was associated with a 42% lower risk for T2DM in women but not in men (p for gender interaction=0.058). Women who were heavy alcohol consumers had a 38% lower risk than abstainers, but this did not reach statistical significance. The protective effect of moderate alcohol consumption on risk of T2DM among women was not attenuated after adjustment for dietary energy density and physical activity in the multivariate model (table 6.6)

In the current results moderate alcohol consumption was associated with lower T2DM risk in women but not in men. The gender differences in the association of alcohol with T2DM may be due to the different social patterning of alcohol consumption between men and women and confounding by SEP (Fillmore et al, 1995). Alternatively, this may arise from gender differences on metabolism of alcohol. A reason for failing to show a harmful effect of heavy alcohol consumption in the current results may be the rather conservative cut-offs for heavy alcohol consumption used (>28 units/week for men; >21 units/week in women) compared to other studies. For example, 5 drinks/day was characterized as heavy drinking in a study (Kao et al, 2001). Another study using more conservative cut-offs however failed to show a harmful effect of heavy drinking indicating as well the importance of the specific cut-offs used to identify heavy drinking (Wannamethee et al, 2003).

Observational epidemiological studies have shown quite consistently that moderate alcohol intake is associated with a lower risk for type 2 diabetes in men and women, while heavy alcohol consumption is associated with an increase in risk (Conigrave et al, 2001; Kao et al, 2001; Wannamethee et al, 2003). Residual confounding may affect such observations as alcohol abstainers (who usually serve as the reference category) are a special category of individuals including many people who abstain from alcohol due to diabetes-related health problems such as obesity and hypertension. Results from a randomized controlled trial however showed that among 51 healthy postmenopausal women, moderate alcohol consumption lowered serum insulin concentrations, suggesting a beneficial effect of moderate alcohol consumption on insulin sensitivity (Davies et al, 2002).

6.4.3.1.4 Smoking

Current smoking was associated with a 2-fold higher risk of T2DM in men but not in women (p for gender interaction=0.033). In the multivariate adjusted model this effect remained robust to adjustments for diet and physical activity. In a well-conducted review of risk factors for T2DM, van Dam (2003) proposed that the smoking-T2DM association is probably the result of residual confounding due to lack of adjustment for physical activity and diet. In the current results the effect of smoking was adjusted for physical activity and diet, but the effect of current smoking on incident T2DM in men remained. The reasons for this gender difference in effect are unclear and are beyond the scope of this project.

Cigarette smoking was associated with increased risk for T2DM in several studies worldwide (Feskens et al, 1989; Rimm et al, 1993; Nakanishi et al, 2000; Wannamethee et al, 2001; Ko et al, 2001). The mechanisms linking smoking to T2DM are still unclear but a reduction of insulin sensitivity through pathways involving endothelial dysfunction and stiffening of the arteries has been suggested.

6.4.3.2 Biological factors and risk of T2DM (Tables 6.9-6.13; Figures 6.1-6.3)

Anthropometric, cardiometabolic and inflammatory factors correlate with each other, thus identifying statistically independent associations is difficult. Correlations between the assessed biological risk factors were first investigated, following by age-adjusted and multivariate-adjusted analysis for identification of factors associated with incident T2DM risk. A correlation matrix showing correlation coefficients between biological variables is presented separately for men and women in tables 6.7 and 6.8 respectively. Results from Cox regression analysis are presented in tables 6.9-6.13.

Table 6.7 Correlations of anthropometric, cardiometabolic and inflammatory factors in the Whitehall II study phase 3 among men

	BMI	blood pressure	triglycerides	HDL	Fibrinogen	CRP	IL-6	vWf	factor VII
Body Mass Index	1.000								
blood pressure	0.255	1.000							
triglycerides	0.373	0.169	1.000						
HDL-cholesterol	-0.303	-0.030	-0.479	1.000					
Fibrinogen	0.216	0.063	0.129	-0.174	1.000				
C-reactive protein	0.120	0.037	0.044	-0.074	0.394	1.000			
Interleukin-6	0.094	0.037	0.047	-0.066	0.252	0.352	1.000		
von Willebrand factor	0.067	0.009	0.032	-0.015	0.153	0.111	0.099	1.000	
factor VII	0.135	0.057	0.182	-0.027	0.053	-0.003	-0.006	-0.040	1.000

Table 6.8 Correlations of anthropometric, cardiometabolic and inflammatory factors in the Whitehall II study phase 3 among women

	BMI	blood pressure	triglycerides	HDL	Fibrinogen	CRP	IL-6	vWf	factor VII
Body Mass Index	1.000								
blood pressure	0.298	1.000							
triglycerides	0.454	0.220	1.000						
HDL-cholesterol	-0.356	-0.052	-0.451	1.000					
Fibrinogen	0.290	0.098	0.170	-0.207	1.000				
C-reactive protein	0.262	0.141	0.161	-0.086	0.383	1.000			
Interleukin-6	0.204	0.125	0.090	-0.081	0.292	0.308	1.000		
von Willebrand factor	0.096	0.094	0.087	-0.033	0.198	0.204	0.103	1.000	
factor VII	0.173	0.111	0.224	-0.053	0.080	0.072	0.039	0.003	1.000

BMI was correlated with most of the biological factors, consistent with the notion that obesity is a condition which markedly alters cardiometabolic risk. Among men, the strongest correlations were observed between BMI and systolic blood pressure (0.26), triglycerides (0.37), HDL (-0.30) and fibrinogen (0.22). Other relatively strong correlations among men were between triglycerides and HDL (-0.49), fibrinogen and CRP (0.39), fibrinogen and IL-6 (0.25), CRP and IL-6 (0.35). Similar findings were observed among women but with some differences. Among women, BMI was more strongly correlated to CRP (0.26) and IL-6 (0.20) than in men. Also the correlation between triglycerides and blood pressure (0.22) was also stronger than in men. The correlations between triglycerides and factor VII (0.22) and CRP and von Willebrand factor (0.20) were also stronger than in men. These correlations confirm that biological factors cluster together, hence independent effects on T2DM risk after mutual adjustment of factors should be interpreted with caution.

6.4.3.2.1 Anthropometric measurements (Table 6.9; Figures 6.1-6.3)

The age-adjusted association between height and 4 obesity measures (1 measure of central obesity and 3 measures of central obesity) and incident T2DM is presented in table 6.9. The results are standardized to aid comparisons between different measures.

Table 6.9 Age-adjusted Hazard Ratios (95% Confidence Intervals) for incident type 2 diabetes per 1 s.dev increase in anthropometric characteristics among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	Hazard Ratios (95% CI)	<i>p-value</i>	Hazard Ratios (95% CI)	<i>p-value</i>
Height (cm)	0.75 (0.62; 0.91)	0.008	0.66 (0.48; 0.91)	0.010
Body Mass Index (kg/m²)	2.07 (1.81; 2.36)	<0.001	1.53 (1.36; 1.72)	<0.001
Waist circumference (cm)	2.18 (1.89; 2.52)	<0.001	1.71 (1.45; 2.01)	<0.001
Waist-hip-ratio	2.47 (2.05; 2.98)	<0.001	2.05 (1.65; 2.54)	<0.001
Waist-height ratio	2.24 (1.96; 2.57)	<0.001	1.66 (1.44; 1.91)	<0.001

6.4.3.2.1.1 Height

Table 6.9 shows that in age-adjusted analysis increasing height had a protective effect on incident T2DM. A standard deviation increase in height was associated with a 25% decrease in risk in men and a 34% decrease in women.

Earlier studies showed consistently that height is associated with risk of cardiovascular disease (Yarnell et al, 1992; Rich-Edwards et al, 1995; Wannamethee et al, 1998; Davey Smith et al, 2000; Jousilahti et al, 2000; Goldbourt et al, 2002; Gunnell et al, 2003; Lawlor et al, 2004) and diabetes (Lawlor et al, 2002; Rudra et al, 2007). Previous evidence showed an association between height and CHD (Langenberg et al, 2005), T2DM (Kumari et al, 2004) and their risk factors (Ferrie et al, 2006) in the Whitehall II study. The pathways linking height to cardiometabolic disease remain elusive. Potential explanations for this association, which may also apply for T2DM risk, include better lung function, insulin-like growth factor axis, vessel diameter, as well as confounding by common risk factors (either genetic or early life) determining both height and cardiometabolic disease (Bobak et al, 1994; Davey Smith et al, 2000; Jarvelin, 2000; Frayling et al, 2002; Wegner et al, 2007).

6.4.3.2.1.2 Obesity measures

For obesity measures, age-adjusted analysis revealed that all obesity measures assessed, namely BMI, waist circumference, waist-hip ratio and waist-height ratio were associated with increased risk of T2DM. For every 1 standard deviation increase in BMI, waist circumference WHR and WHtR there was a more than 2-fold increase in the risk for T2DM in men while in women the effect was slightly weaker, around 1.5-fold higher risk.

In order to investigate whether central obesity measures were better than BMI at predicting incident T2DM cases, ROC analysis for variable comparison was used. Three variables of central obesity (waist circumference, WHR and WHtR) were individually compared with BMI in age-adjusted ROC analysis. The results are shown in figures 6.1-6.3.

Figure 6.1 ROC curves showing area under curve (AUC) for comparing the predictive power of BMI against waist circumference in Cox regression analysis among men and women

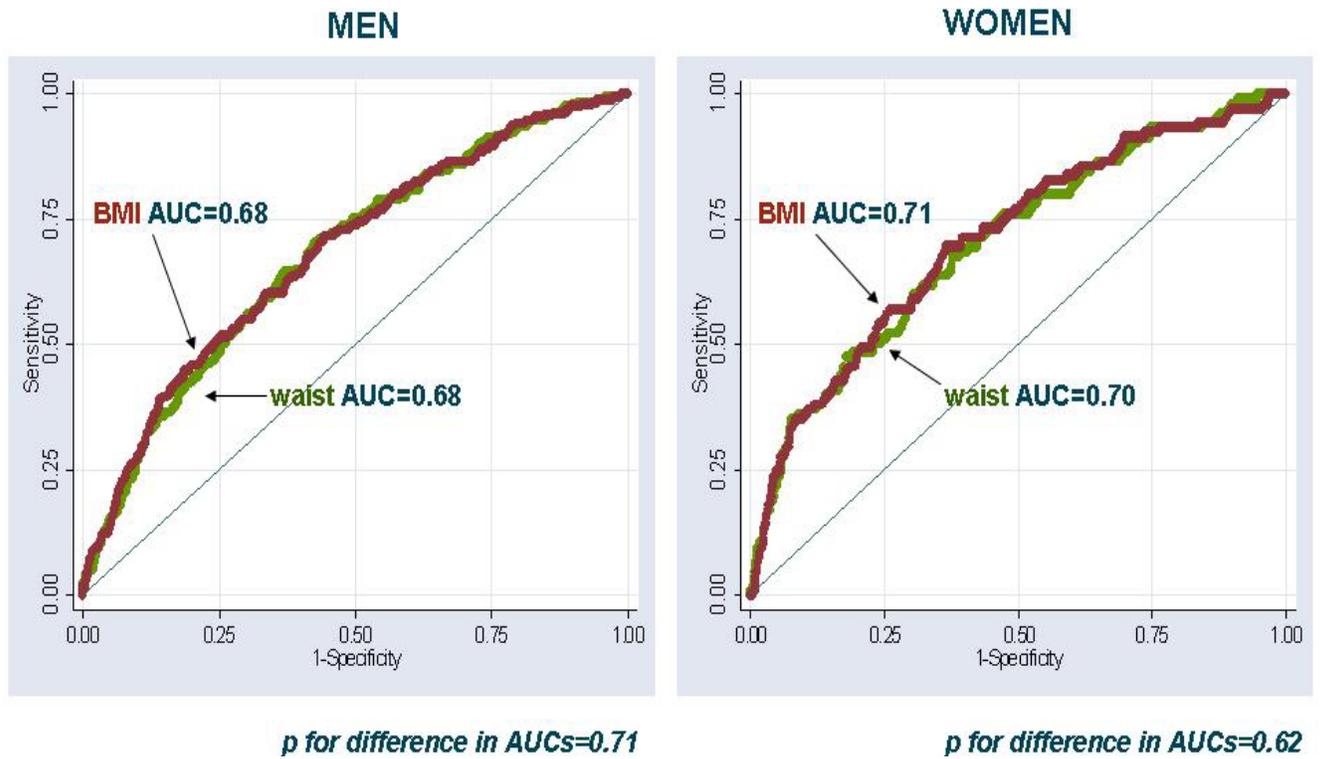


Figure 6.1 shows that there is no difference between baseline (phase 3) BMI and waist circumference in predicting incident T2DM cases among men and women in the WII study.

Figure 6.2 ROC curves showing area under curve (AUC) for comparing the predictive power of BMI against waist-hip ratio in Cox regression analysis among men and women

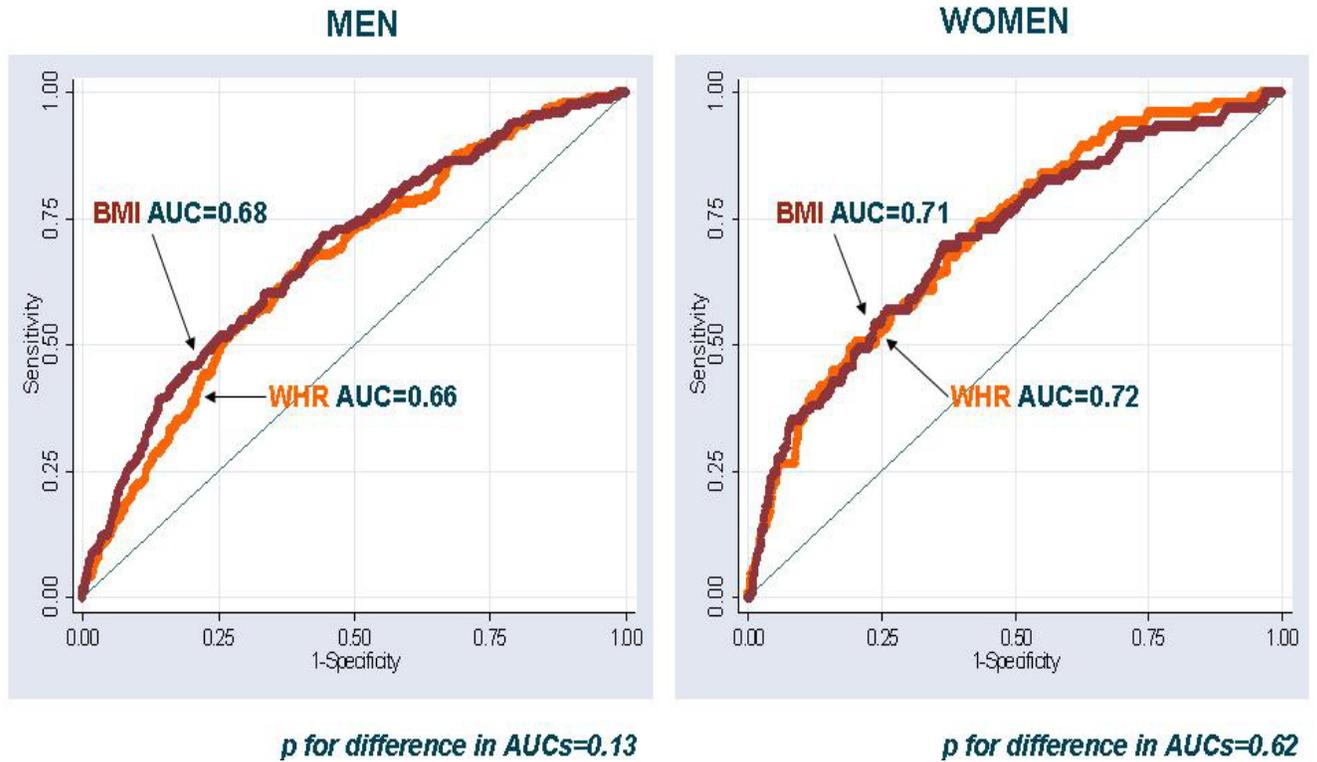


Figure 6.2 shows that, among men, WHR is inferior to BMI in predicting incident T2DM cases (AUC=0.66 vs. 0.68), but this difference did not reach statistical significance. Among women, WHR was slightly better than BMI in predicting incident cases (AUC=0.72 vs. 0.71), but again this did not reach statistical significance.

Figure 6.3 ROC curves showing area under curve (AUC) for comparing the predictive power of BMI against waist-height ratio in Cox regression analysis among men and women

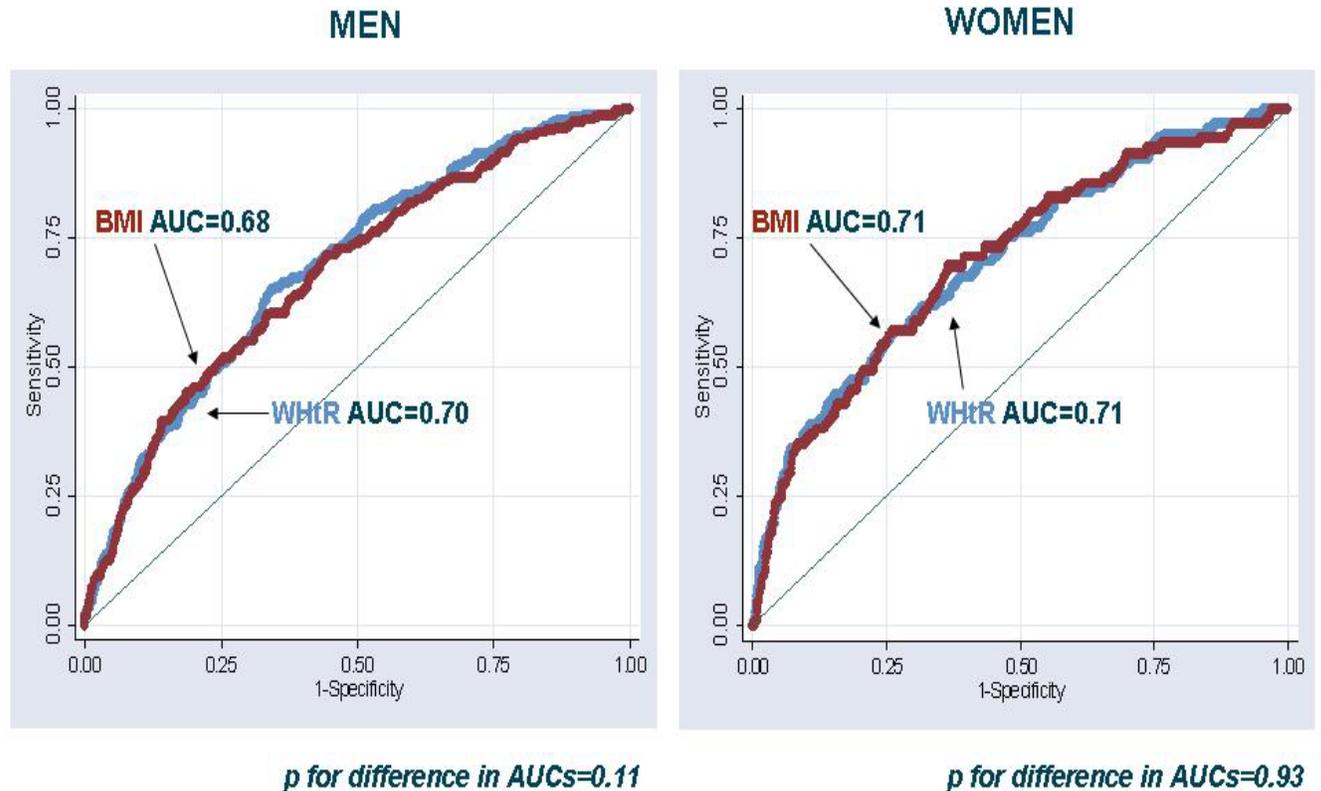


Figure 6.3 shows that, among men, WHtR is superior to BMI in predicting incident T2DM cases (AUC=0.70 vs. 0.68), but this difference did not reach statistical significance. Among women, BMI and WHtR did not differ in predicting incident cases.

Overall, there was no evidence that central obesity measures are better at predicting incident T2DM cases than BMI among Caucasian men and women in the WII study. WHR among women and WHtR among men slightly improved the prediction of BMI (not significant differences) but BMI will be used as the obesity measure in further analysis due to its wider use in the literature and defined cut-offs points.

6.4.3.2.2 Cardiometabolic factors (Table 6.10)

Table 6.10 shows age-adjusted associations between baseline (phase 3) cardiometabolic factors and risk of T2DM among men and women.

Table 6.10 Age-adjusted Hazard Ratios (95% Confidence Intervals) for incident type 2 diabetes per 1 s.dev increase in cardiometabolic and inflammatory factors among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	Hazard Ratios (95% CI)	<i>p</i> -value	Hazard Ratios (95% CI)	<i>p</i> -value
Systolic blood pressure (mmHg)	1.31 (1.15; 1.50)	<0.001	1.50 (1.23; 1.83)	<0.001
Triglycerides (mmol/L)	1.22 (1.16; 1.27)	<0.001	1.83 (1.52; 2.20)	<0.001
HDL-cholesterol (mmol/L)	0.53 (0.44; 0.64)	<0.001	0.59 (0.47; 0.74)	<0.001

6.4.3.2.2.1 Blood pressure

In age-adjusted analysis (table 6.10), blood pressure showed the expected direct association with T2DM risk. In men, every increase in 1 standard deviation in systolic blood pressure was associated with a 30% higher risk of T2DM, while in women the effect rose to 50% higher risk.

Other prospective studies have attempted to clarify whether blood pressure precedes or coexist with T2DM by investigating risk of T2DM by baseline blood pressure found that high blood pressure was a risk factor for T2DM (Conen et al, 2007; Golden et al, 2003; Doteval et al, 2004). In some of these studies there was a reduction in the effect of blood pressure on incident T2DM after adjusting for BMI, but the effect was not abolished.

6.4.3.2.2.2 Blood lipids

A one standard deviation increase in triglyceride levels was associated with a 22% increased risk for T2DM in men and 83% increased risk in women. HDL-cholesterol was linearly associated with a decreased risk for T2DM. Every increase in 1 standard deviation of HDL-cholesterol was associated with ~40% decrease in T2DM risk in men and women.

High levels of blood triglycerides have been associated with an increased risk for T2DM (Steiner, 1986; Meigs et al, 2004). Prospective epidemiological studies have shown a strong effect of baseline triglyceride levels on future risk of T2DM (Kametani et al, 2002; Love-Osborne et al, 2006). Obesity is a major potential

confounder in the association between triglyceride level and T2DM. Similar findings were observed in a study among Swedish women, in which among several risk factors for T2DM, including physical activity and blood pressure, triglycerides showed the strongest link with incident T2DM even after adjusting for other cardiometabolic risk factors (Doteval et al, 2004). Like the current findings, this effect of triglycerides was stronger in men than in women.

6.4.3.2.3 Inflammatory markers (Table 6.11)

Table 6.11 shows age-adjusted associations between baseline (phase 3) cardiometabolic and inflammatory factors and risk of T2DM among men and women.

Table 6.11 Age-adjusted Hazard Ratios (95% Confidence Intervals) for incident type 2 diabetes per 1 s.dev increase in inflammatory factors among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	Hazard Ratios (95% CI)	<i>p-value</i>	Hazard Ratios (95% CI)	<i>p-value</i>
Fibrinogen	1.26 (1.10; 1.45)	<i>0.001</i>	1.38 (1.15; 1.64)	<i><0.001</i>
C-reactive protein	1.15 (1.08; 1.22)	<i><0.001</i>	1.15 (1.06; 1.26)	<i><0.001</i>
Interleukin-6	1.07 (0.98; 1.17)	<i>0.13</i>	1.13 (0.98; 1.31)	<i>0.09</i>
von Willebrand factor	1.20 (1.05; 1.38)	<i><0.001</i>	1.08 (0.88; 1.34)	<i>0.46</i>
factor VII	1.12 (1.03; 1.22)	<i>0.010</i>	1.11 (0.94; 1.32)	<i>0.23</i>

All inflammatory markers assessed were associated with incident T2DM apart from IL-6 in men and von Willebrand factor and factor VII in women.

In the ARIC study, among other markers, fibrinogen was found to be predictive of T2DM (Schmidt et al, 1999; Duncan et al, 1999). Similar evidence came from the US Women’s Health Study, the US Cardiovascular Health Study and the Nurses’ Health Study for CRP and IL-6 (Pradhan et al, 2001; Vozarova et al, 2002; Hu et al, 2004). Associations were also found in the US Insulin Resistance and Atherosclerosis Study (Festa et al, 2002), in the West of Scotland Coronary Prevention Study (Freeman et al, 2002), in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Postdam Study in Germany (Spranger et al, 2003), in the MONICA Augsburg Study

in Germany (Thorand et al, 2003) and among a cohort of Finnish adults (Hu et al, 2009).

Two studies found gender differences in the association between inflammatory markers and T2DM. In the Mexico City Diabetes Study, CRP was associated with T2DM in women but not in men (Han et al, 2002), while in the MONICA/KORA study in Germany activation of innate immunity increased the risk of T2DM only in women.

6.4.3.2.4 Cardiometabolic and inflammatory factors showing statistically independent associations with T2DM (Table 6.12 and 6.13)

The correlation between biological factors makes it difficult to disentangle their effects as including them simultaneously in a model can be statistically inappropriate due to collinearity. In order to deal with this issue, backwards modelling was performed in addition to multivariate adjusted analysis.

The principles of backwards modelling were described in the methods chapter, subsection 4.3.3.6.2. Briefly, backwards modelling involved subsequent exclusion of variables from the maximally adjusted Cox regression model, containing triglycerides, blood pressure, HDL-cholesterol and inflammatory markers and performing a statistical test for the effect on the predictive power of the model each time a variable (or group of variables) is removed.

Table 6.12 Adjusted* Hazard Ratios (95% Confidence Intervals) for incident type 2 diabetes per 1 s.dev increase in cardiometabolic and inflammatory factors among men and women after 15 years of follow-up in the Whitehall II study

	MEN		WOMEN	
	Hazard Ratios (95% CI)	<i>p</i> -value	Hazard Ratios (95% CI)	<i>p</i> -value
Systolic blood pressure (mmHg)	1.26 (1.07; 1.47)	0.005	1.45 (1.15; 1.83)	0.004
Triglycerides (mmol/L)	1.32 (1.15; 1.52)	<0.001	1.40 (1.02; 1.93)	0.015
HDL-cholesterol	0.70 (0.55; 0.89)	0.003	0.77 (0.57; 1.05)	0.095
Fibrinogen	1.13 (0.95; 1.34)	0.16	1.30 (1.02; 1.65)	0.032
C-reactive protein	1.12 (1.02; 1.22)	0.009	1.08 (0.91; 1.28)	0.36
Interleukin-6	0.98 (0.82; 1.17)	0.69	1.02 (0.84; 1.25)	0.81
von Willebrand factor	1.19 (1.02; 1.37)	0.025	0.93 (0.73; 1.19)	0.57
factor VII	1.06 (0.92; 1.20)	0.42	1.09 (0.88; 1.36)	0.41

*mutually adjusted

After adjustment for triglycerides, HDL-cholesterol and inflammatory markers in the multivariate adjusted biological model (table 6.12) the effect of systolic blood pressure on incident T2DM remained robust, with the effect being stronger among women.

After adjusting for systolic blood pressure, HDL-cholesterol and inflammatory markers, the effect of triglycerides was increased to 32% higher risk in men but was reduced to 40% higher risk in women. This gender difference means that in men, in the unadjusted model, the effect was diluted by some other covariate, which was then included in the mutually adjusted model, while in women another covariate confounded the initial unadjusted effect and hence the decrease in risk in the adjusted model. After adjustment for blood pressure, triglycerides and inflammatory markers, the effect of 1 standard deviation increase in HDL was 30% risk reduction in men and 23% in women.

Inclusion of cardiometabolic factors with inflammatory factors in the multivariate adjusted biological model, attenuated most of the effect of inflammatory markers. Only CRP and fibrinogen were associated with incident T2DM. The results differed by gender in that in men only the CRP effect (12% increase in risk each increase in 1 standard deviation) reached statistical significance and the fibrinogen effect was

marginally non-significant, while in women it was vice versa, with a 30% increase in risk for each increase in 1 standard deviation in fibrinogen level.

Table 6.13 Results from backwards modelling showing the effect of subsequent removal of variables from the maximally adjusted cardiometabolic and inflammatory model on incident type 2 diabetes

Cox regression model	<i>LRT p-value for difference in model</i>		
	MEN	WOMEN	WHOLE SAMPLE
triglycerides + blood pressure + HDL +inflammatory markers removing inflammatory markers	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>
removing HDL	0.008	0.13	<0.001
removing blood pressure	0.001	0.035	0.002
	0.007	0.001	<0.001

Table 6.13 shows the effect on the model of removing a variable (or group of variables) from the multivariate adjusted biological model. Backwards modelling showed that removing blood pressure and HDL from the maximally adjusted model resulted in lowering of the predictive power of the model in both men and women. Removing of inflammatory markers also made a difference but this reached statistical significance only in men. Removal of inflammatory markers did reach statistical significance in the whole sample and thus it is concluded that the lack of statistical significance in women was due to the small sample size. This analysis suggests that, in addition to triglycerides, HDL-cholesterol, systolic blood pressure and inflammatory markers are (statistically) independently associated with incident T2DM.

Overall, biological factors were strongly associated with incident T2DM. Central obesity measures were not more predictive than BMI for incident T2DM. Triglycerides had a strong independent association with incident T2DM. Blood pressure and HDL-cholesterol were also independently associated with incident T2DM, with the effect of blood pressure being stronger in women and the effect of HDL-cholesterol being stronger in men. Inflammatory markers as a group improved the model containing only cardiometabolic factors for predicting T2DM. It was

therefore decided that all the assessed biological factors will be used as potential mediating factors in the work stress-incident T2DM association (chapter 9).

Similar findings were found by a UK study looking at prospective associations between behavioural and biological factors and incident T2DM among middle-aged British men (Perry et al, 1995). These authors found that BMI and physical activity were major risk factors for T2DM, while evidence for an association for alcohol consumption and smoking was weaker. Like the current results, triglyceride level was a strong predictor of T2DM among men, while systolic blood pressure was not. Another study in Australia found that, as in the current results, there was a protective effect of moderate alcohol consumption and a harmful effect of high blood pressure on T2DM risk among women (Strodi & Kenardy, 2006).

A summary table of results for associations between socioeconomic, psychosocial, behavioural and biological factors with incident T2DM is given in appendix 5. The strength of the association is also indicated in the appendix. The variables not appearing in appendix 5 were not associated with incident T2DM in either men or women

6.5 Summary and link to next chapter

1. Employment grade was associated with incident T2DM in both men and women and was chosen as the SEP measure to be used in further analysis in the current project. From the psychosocial and psychological characteristics assessed, the degree upset by life events was the sole predictor of incident T2DM. Among health behaviours, physical activity was inversely associated with incident T2DM. In men, an unhealthier dietary pattern and in women higher dietary energy density were associated with T2DM risk. Moderate alcohol consumption was associated with lower risk in women, while current smoking was associated with an increased risk in men. Height and obesity were strongly linked to incident T2DM. Blood pressure, triglycerides HDL and inflammatory markers were also associated with incident T2DM.

2. Measures of central obesity (WHR, WHtR, waist circumference) were similar to BMI in predicting incident T2DM cases. BMI was chosen to be used for further analysis.
3. Blood pressure, triglyceride levels and HDL-cholesterol levels were (statistically) independently associated with incident T2DM. Inflammatory markers improved a model containing these cardiometabolic risk factors for predicting incident T2DM.

Potential confounding and mediating variables in the work stressors-incident T2DM association have been identified in this chapter. The association between psychosocial work stressors and incident T2DM after adjusting for potential confounders is investigated in the next chapter (chapter 7). The association between psychosocial work stressors and incident T2DM after adjusting for potential mediators is investigated in chapter 9.

Chapter 7: Effect of psychosocial work stressors on risk of type 2 diabetes

7.1 Introduction

The stressful experience at work is a complex and subjective experience so it is essential to identify the 'toxic' components involved. This can be achieved with the help of theoretical models. Two such models have received special attention and were widely used in the literature. The demand/control/support model posits that high psychological demands at work in combination with low control, in terms of skill utilisation and decision latitude, elicit sustained high stress in the workplace (Karasek, 1979). This model is widely known as the job strain model. Iso-strain is an extension of the job strain model and hypothesizes that socially isolated workers (i.e., without supportive coworkers or supervisors) simultaneously experiencing job strain, carry the highest risk for disease (Johnson and Hall, 1988; Landsbergis et al, 1994).

The effort-reward imbalance model is an alternative theoretical model also developed to measure psychosocial stress at work. The theoretical approach of the ERI model is characterized by mutual cooperative investments based on the norm of return expectancy where efforts are equalized by respective rewards. Failed reciprocity in terms of high efforts spent and low rewards received is likely to elicit recurrent negative emotions and sustained stress responses in exposed people (Siegrist et al, 1986). Both the demand/support/control and ERI models are described in more detail in chapter 1 of this thesis.

Based on the above, psychosocial work stressors have the potential to increase risk of T2DM. Age could confound the work stress-incident T2DM association, as age is associated with T2DM incidence and work stressors. Other aspects of the social environment, such as socioeconomic position and psychosocial factors outside work are associated with both work stressors and T2DM, thus they could confound the effect of work stressors on incident T2DM. Finally, height can be regarded as reflecting adversity in early life (*in utero* or early childhood) (Jarvelin, 2000; Langenberg et al, 2005; Webb et al, 2008). Both T2DM and reporting of exposure to

work stressors may share a common risk factor (childhood adversity in this case) which precedes the two conditions. In other words, something that occurred in early life (and for which height may be a non-specific marker) may influence both people's response to stressors and the development of T2DM and confound the observed association between the two later in life.

In order for a variable to be identified as a potential confounder in statistical terms, it needs to be associated with both the exposure and the outcome of interest. Evidence for the association between the potential confounders described above and incident T2DM can be found in chapter 6. The association between these potential confounders and work stressors is assessed in the current chapter.

Previous studies looking at the effect of work stressors on T2DM identified a gender difference, with the effect of work stressors based on the demand/control/support model being apparent in women but not in men (see systematic review, chapter 2). This effect modification by gender is also addressed in the current project. Age, socioeconomic position and obesity also have the potential to modify the effect of psychosocial work stressors on incident T2DM. It has previously been shown that the effect of work stressors may be higher in younger rather than older ages among middle-aged individuals (Chandola et al, 2008). The working role may be more important in younger employees rather than older ones. Social vulnerability refers to the condition in which past or present social disadvantage modifies the effect of other insults on disease (Blane, 2006). In the case of the current project, civil service employment grade is used as an indicator of socioeconomic position (Marmot et al, 1991) and low employment grade as a marker of social vulnerability. Biological vulnerability may refer to a poor health status that renders an individual at increased risk of other insults. In the case of T2DM, obesity is a good indicator of biological vulnerability as obesity is the most important risk factor of the disease.

7.2 Chapter aim, objectives and main hypotheses

Aim:

To investigate the effect of psychosocial work stressors on risk of T2DM, adjusting for and stratifying by other covariates.

Objectives:

1. To identify potential confounders for the psychosocial work stressors-incident T2DM association by determining associations between work stressors and sociodemographic and psychosocial factors linked to T2DM.
2. To examine the age-adjusted and multivariate adjusted association between 2 different psychosocial work stress models and their component scales and incident T2DM from WII phase 3 (1991-93) to phase 7 (2002-04).
3. To assess effect modification in the association between psychosocial work stressors and incident T2DM by gender, age, employment grade and obesity.

Main hypotheses:

1. Psychosocial work stressors increase the risk of T2DM among middle-aged men and women after adjustment for sociodemographic and psychosocial stressors outside work.
2. The effect of psychosocial work stressors on incident T2DM is modified by gender, age, employment grade and obesity.

7.3 Chapter methodology

7.3.1 Sample description

The specific sample used in the current analysis is the one used in the previous chapter on risk factors for T2DM. For detailed description of the exclusion criteria refer to chapter 6, section 6.2.1. In summary, 5895 Caucasian participants (4166 men, 1729 women) with data on psychosocial work stressors and T2DM follow-up and who were not diabetics at WII phase 3 (analysis baseline) were selected for analysis.

7.3.2 Variables used in current chapter

The variables used in the current chapter, together with the sub-section in which they were described in the methods section, are listed below:

7.3.2.1 Main exposures and outcome

- High job demands (4.2.2.2.1)
- Low job control (4.2.2.2.1)
- Low work social support (4.2.2.2.1)
- Job strain (4.2.2.2.1)
- Iso-strain (4.2.2.2.1)
- Efforts at work (4.2.2.2.2)
- Rewards at work (4.2.2.2.2)
- Effort-reward imbalance (4.2.2.2.2)
- Incident T2DM (4.2.2.1)

7.3.2.2 Potential confounders or effect modifiers

- Age (4.2.2.3.2)
- Employment grade (4.2.2.3.2)
- Degree upset by life events (4.2.2.4.2)
- Body Mass Index (4.2.2.6.1.1)
- Height (4.2.2.6.1.1)

For the demand/control/support model, all individual components were dichotomized (high job demands; low job control; low work social support) (see methods chapter, sub-section 4.2.2.2.1). For the ERI model, individual components as well as the ERI scale were used both as continuous and as binary variables. The reason for this, is that work stressors based on the demand/control/support model have been used only as categorical variables in the literature (Belkic et al, 2004), while work stressors based on the ERI model have been used as a scale (Kuper et al, 2002) and categorised (Bosma et al, 1998).

In order to statistically test interactions between psychosocial work stressors and the variables described in this chapter's introduction, variables were dichotomised in the following way: age (<50 years vs. ≥50 years); employment grade (high/middle vs. low); obesity ($BMI \geq 30 \text{ kg/m}^2$ vs. $BMI < 30 \text{ kg/m}^2$).

7.3.3 Statistical analysis

7.3.3.1 Crude survival analysis for the effect of work stressors on incident T2DM

Initially, survival analysis was used to estimate the crude incident rate of T2DM between 1991-2004 (methods chapter, sub-section 4.3.2.3). The sample used in the current chapter is different from that used for survival analysis in chapter 5. Survival probabilities were plotted stratifying by the work stressor variables using Kaplan-Meier curves (sub-section 4.3.2.3).

7.3.3.2 Adjusted hazard ratios for the effect of work stressors on incident T2DM

Cox proportional hazards regression models (methods chapter, sub-section 4.3.4.3) were used in order to investigate the association between baseline psychosocial work stressors and incident T2DM, from 1991 (beginning of phase 3) to 2004 (end of phase 7), adjusting for potential confounding variables. The maximum follow-up time during this period was 14.7 years. Cox regression models were estimated for three different work stressor variables, namely job strain, iso-strain and effort-reward imbalance, as well as the components of these work stress variables, namely job demands, job control, social support at work, efforts at work and rewards at work.

The base model in the Cox regression analysis with incident T2DM as the outcome variable and psychosocial work stressors as exposure variables (separate models were estimated for each psychosocial work characteristic variable) was adjusted for age. A second model was adjusted for age and employment grade (age + SEP model). The rationale for the 'age+SEP' model was to account for the role of socioeconomic circumstances in the association between psychosocial work stressors and T2DM. Finally, a third model was adjusted for the degree upset by life events and height. The rationale behind this final adjustment was that people who reported more adverse

psychosocial work characteristics (and hence more work stress) are people who were affected by adverse life events that happened in the recent past and/or people that were exposed to childhood adversity. Cox regression models for dealing with potential confounding were estimated in the following way:

Model 1:

$$h(t) = h_0(t) * \exp(\beta_1 \text{work stressor} + \beta_2 \text{age})$$

Model 2:

$$h(t) = h_0(t) * \exp(\beta_1 \text{work stressor} + \beta_2 \text{age} + \beta_3 \text{employment grade})$$

Model 3:

$$h(t) = h_0(t) * \exp(\beta_1 \text{work stressor} + \beta_2 \text{age} + \beta_3 \text{employment grade} + \beta_4 \text{life events} + \beta_5 \text{height})$$

Further adjustments for other T2DM risk factors (identified in chapter 6) will be presented in a separate chapter looking at potential mediating factors in the association between psychosocial work stressors and incident T2DM (chapter 9).

7.3.3.3 Statistical tests for interaction between work stressors and other variables

Interactions were tested between the psychosocial work stressors (job strain, iso-strain and ERI) and sex, age, employment grade and baseline body weight status, using the likelihood ratio test (LRT). The rationale behind these statistical tests for interaction was to generate evidence on the second hypothesis of the current chapter, that the effect of psychosocial work stressors on incident T2DM was modified by other factors.

7.4 Distribution of work stressors among WII participants and associations with potential confounders

7.4.1 Distribution of work stressors among men and women in the WII study (1991-93)

Table 7.1 below shows the prevalence of components of the demand/control/support and ERI models, as well as prevalence of the 3 work stressor measures derived from these models.

Table 7.1 Distribution of psychosocial work stressor variables and their components among men and women selected for analysis at WII phase 3

	MEN (N=4192)		WOMEN (N=1729)		<i>p for gender difference</i>
	N	%	N	%	
High job demands	2222	53.3	756	43.7	<0.001
Low job control	1846	44.3	1171	67.7	<0.001
Low work social support	1377	33.3	585	34.0	0.64
Job strain	987	24.7	512	31.2	<0.001
Iso-strain	475	12.0	241	15.0	0.002
High efforts at work	1408	33.8	793	45.9	<0.001
Low rewards at work	1266	30.8	583	34.1	0.013
High effort-reward imbalance	481	11.7	297	17.4	<0.001

From table 7.1 it is clear that women overall report more adverse working conditions, which is reflected by the higher prevalence of adverse psychosocial work characteristics (high efforts at work; low job control and rewards at work) compared to men. The only exception is prevalence of high job demands, which is higher among men, and low social support at work, which is similar in men and women. Prevalence of psychosocial work stressors is much higher in women than men. Job strain affects around 31% of women compared to around 25% of men, while iso-strain affects 15% of women compared to 12% of men. High ERI affects around 17% of women compared to around 12% of men (all p-values for gender differences <0.05).

7.4.2 Association between work stressors and potential confounders in the association with incident T2DM

The association between potential confounders and psychosocial stress at work variables can be found in tables 7.2 and 7.3.

Table 7.2 Prevalence of job strain, iso-strain and their components by categories of the main confounding variables at analysis baseline (1991-93) among the Whitehall II participants selected for analysis

	MEN (N=4192)					WOMEN (N=1729)				
	high job demands	low job control	low work social support	job strain	iso-strain	high job demands	low job control	low work social support	job strain	iso-strain
Age group	% (number)	% (number)	% (number)	% (number)	% (number)	% (number)	% (number)	% (number)	% (number)	% (number)
39-44	54.5 (680)	47.5 (593)	35.6 (443)	28.7 (340)	14.4 (170)	50.2 (212)	55.2 (233)	36.8 (154)	27.6 (107)	13.0 (157)
45-49	56.0 (705)	44.0 (554)	33.1 (414)	23.5 (283)	12.0 (143)	50.0 (228)	66.2 (302)	34.7 (158)	34.3 (142)	16.0 (190)
50-54	54.5 (448)	42.3 (348)	34.6 (282)	24.3 (193)	11.0 (87)	45.3 (169)	72.7 (271)	39.0 (145)	36.7 (128)	17.0 (207)
55-63	46.4 (389)	41.9 (351)	29.0 (238)	20.9 (171)	9.3 (75)	30.8 (147)	76.4 (365)	26.9 (128)	29.7 (135)	12.0 (147)
<i>p-value</i>	<i><0.001</i>	<i>0.036</i>	<i>0.016</i>	<i>0.001</i>	<i>0.006</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>	<i>0.027</i>	<i>0.001</i>
Employment grade										
High	65.0 (1370)	27.1 (571)	31.9 (664)	18.1 (370)	9.1 (184)	77.6 (242)	27.9 (87)	37.9 (118)	20.6 (59)	10.0 (200)
Middle	44.1 (805)	58.1 (1061)	34.2 (620)	32.1 (558)	15.0 (260)	46.6 (382)	65.8 (539)	37.4 (305)	37.6 (284)	19.0 (380)
Low	19.2 (44)	93.0 (213)	39.5 (90)	27.2 (59)	14.4 (31)	22.1 (132)	91.1 (545)	27.2 (162)	30.0 (169)	11.0 (220)
<i>p-value</i>	<i><0.001</i>	<i><0.001</i>	<i>0.040</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>	<i><0.001</i>
Life events										
T1	49.4 (651)	45.5 (599)	29.7 (388)	23.0 (288)	10.5 (130)	40.6 (166)	65.5 (268)	31.6 (129)	28.9 (108)	12.0 (150)
T2	55.0 (580)	41.1 (434)	32.7 (342)	23.8 (242)	11.4 (115)	47.4 (146)	63.6 (196)	33.0 (101)	33.5 (94)	15.0 (150)
T3	55.8 (953)	45.4 (776)	36.5 (619)	26.7 (443)	13.5 (222)	45.4 (425)	68.7 (644)	35.0 (326)	32.8 (289)	16.0 (300)
<i>p-value</i>	<i>0.001</i>	<i>0.054</i>	<i><0.001</i>	<i>0.051</i>	<i>0.040</i>	<i>0.14</i>	<i>0.20</i>	<i>0.22</i>	<i>0.33</i>	<i>0.001</i>
Height tertiles										
T1	49.5 (620)	48.0 (601)	33.9 (421)	25.8 (311)	13.3 (159)	38.3 (200)	74.5 (389)	31.5 (164)	32.7 (160)	14.0 (140)
T2	55.1 (791)	43.2 (621)	33.7 (481)	23.8 (329)	11.0 (152)	43.8 (254)	67.1 (389)	33.6 (194)	32.4 (173)	15.0 (150)
T3	55.0 (807)	42.1 (618)	32.5 (471)	24.5 (344)	11.7 (162)	48.3 (302)	62.6 (391)	36.6 (227)	30.9 (179)	15.0 (150)
<i>p-value</i>	<i>0.004</i>	<i>0.006</i>	<i>0.70</i>	<i>0.51</i>	<i>0.21</i>	<i>0.003</i>	<i><0.001</i>	<i>0.19</i>	<i>0.79</i>	<i>0.001</i>

Prevalence of high job demands and low work social support decreased with increasing age in both men and women, while prevalence of low job control decreased in men but increased in women. Job strain and iso-strain decreased gradually with increasing age in men, but in women the prevalence increased in the age range 45-54 but decreased in the oldest age-group (55-63).

Prevalence of high job demands decreased considerably from high employment grade to medium grade to low. Prevalence of low job control increased considerably from high to low grades. Prevalence of low work social support differed by gender in that it increased from high to low grade among men but decreased among women. The lowest prevalence of job strain and iso-strain was observed in the high employment grade in both men and women but, unexpectedly, prevalence was higher in the middle compared to the low grade. Prevalence of iso-strain was similar in the middle and low grades in men.

Prevalence of high job demands and low work social support increased as the degree participants were upset by life events increased, but only in men. Prevalence of job strain and iso-strain increased with increasing degree upset by life events, but the difference only reached statistical significance in men.

Prevalence of high job demands increased, while prevalence of low job control decreased with increasing height in both men and women. Prevalence of job strain and iso-strain however did not differ by height.

Table 7.3 Associations between effort-reward imbalance and its components with the main confounding variables at analysis baseline (1991-93) among the Whitehall II participants selected for analysis

	MEN (N=4192)			WOMEN (N=1729)		
	high efforts at work	low rewards at work	high ERI	high efforts at work	low rewards at work	high ERI
Age group	% (number)	% (number)	% (number)	% (number)	% (number)	% (number)
39-44	36.3 (453)	40.3 (500)	12.6 (156)	38.6 (163)	25.1 (154)	21.7 (57)
45-49	33.9 (426)	37.0 (461)	11.4 (142)	44.1 (201)	26.3 (161)	23.3 (61)
50-54	32.2 (265)	36.5 (295)	10.3 (83)	47.9 (178)	20.7 (127)	21.8 (57)
55-63	31.6 (264)	34.2 (279)	9.0 (73)	52.7 (251)	27.9 (171)	33.2 (87)
<i>p-value</i>	0.015	0.006	0.016	<0.001	0.81	0.095
Employment grade						
High	23.2 (489)	33.3 (691)	6.6 (136)	24.7 (77)	27.1 (84)	6.1 (19)
Middle	41.2 (751)	41.4 (748)	13.8 (249)	41.6 (340)	36.1 (291)	14.5 (117)
Low	72.8 (166)	41.6 (94)	30.2 (68)	63.1 (376)	40.2 (238)	21.3 (126)
<i>p-value</i>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Upset by life events tertiles						
T1	36.1 (475)	36.8 (478)	12.2 (158)	45.0 (184)	36.1 (146)	15.6 (63)
T2	33.5 (353)	35.8 (373)	9.5 (99)	43.0 (132)	35.1 (106)	14.6 (44)
T3	31.7 (541)	38.7 (652)	11.1 (186)	46.6 (436)	36.7 (334)	15.4 (143)
<i>p-value</i>	0.012	0.25	0.31	0.48	0.95	0.88
Height tertiles						
T1	33.7 (421)	38.8 (480)	11.1 (137)	49.1 (256)	38.5 (199)	17.6 (91)
T2	33.4 (479)	36.8 (523)	11.8 (167)	47.6 (275)	35.7 (204)	14.0 (80)
T3	34.4 (504)	36.7 (530)	10.3 (149)	41.6 (260)	34.0 (210)	14.8 (91)
<i>p-value</i>	0.66	0.27	0.23	0.009	0.12	0.002

Table 7.3 shows association between high efforts at work, low rewards at work and high ERI and potential confounders in the association with incident T2DM (age, employment grade, life events and height). High efforts at work decreased with increasing age in men but increased in women. Low rewards at work also decreased with increasing age in men but remained unchanged in women. High ERI increased with increasing age in both men and women. High efforts and low reward at work increased from high to low grades in both men and women. Similarly, high ERI increased from high to low employment grade in both men and women. ERI and its components were not associated with the degree

upset by life events, apart from a small decrease in high efforts at work with increasing life events among men. ERI and its components were not associated with height among men. Among women there was a decrease in high efforts at work and high ERI with increasing height.

Overall, among the variables identified as potential confounders in the work stressors-incident T2DM association from chapter 6, only age and employment grade showed consistent associations with components of the demand/control/support and ERI models in both men and women. Life events and height were more weakly and inconsistently associated with work stressors. Despite these weaker associations, all the above variables were selected for inclusion in multivariate adjusted analysis in the current chapter.

7.5 Survival probability and incidence rate of T2DM by work stress

Incidence rates for T2DM per 1000 person-years during follow-up, stratifying by each of the psychosocial work stressors, are shown in table 7.4.

Table 7.4 Crude incident rates of type 2 diabetes by baseline psychosocial work stressors during 15 years follow-up in the Whitehall II study

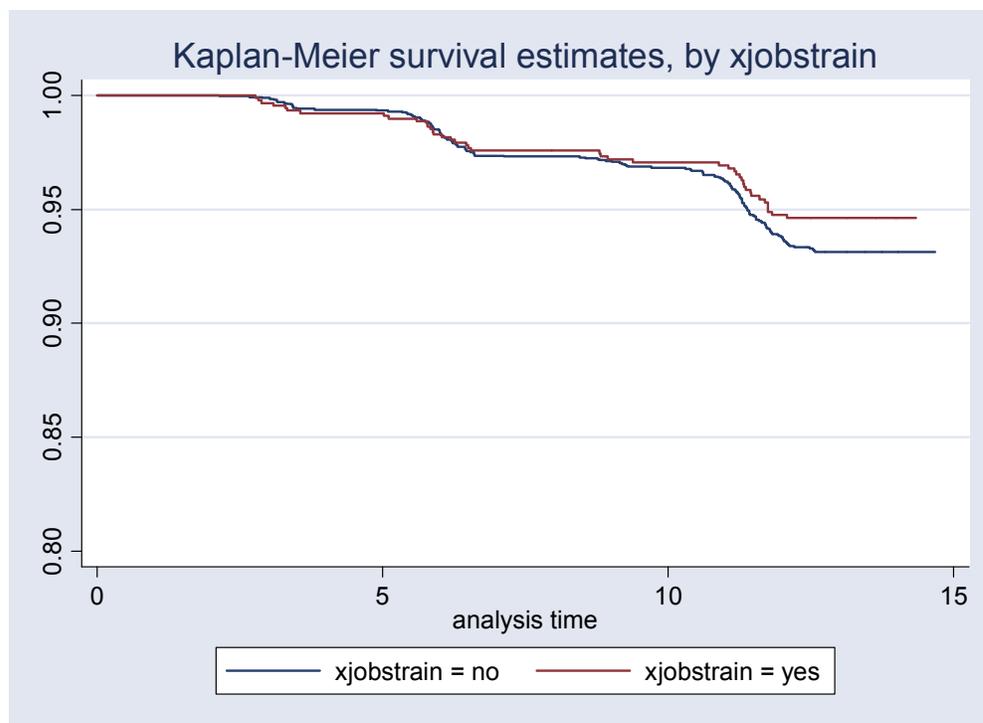
	T2DM cases	Person-years at risk	Rate (per 1000 p-y)	95% CI
No job strain	225	46 246	4.87	4.27 – 5.54
Job strain	65	13 185	4.93	3.87 – 6.29
No iso-strain	257	54 310	4.73	4.19 – 5.35
Iso-strain	36	6480	5.56	4.01 – 7.70
ERI				
Low efforts AND high rewards	91	18 236	4.99	4.06 – 6.13
High efforts OR low rewards	104	21 972	4.73	3.91 – 5.74
High efforts AND low rewards	17	5011	3.39	2.11 – 5.46

The crude incidence rate of T2DM was higher in participants exposed to job strain and iso-strain compared to those non-exposed. Participants exposed to high ERI (high efforts AND low rewards) had a lower rather than a higher rate of T2DM. The confidence

intervals of these differing incidence rates overlapped. Results from multivariate adjusted Cox regression analysis, presented in section 7.6, are more informative on differences in incidence in those exposed and not exposed to work stressors.

Figures 7.1-7.6 show Kaplan-Meier survival probabilities for the risk of T2DM during follow-up by baseline psychosocial work stressors (job strain, iso-strain and ERI) for men and women respectively. The log-rank test tests whether the two curves (not exposed vs. exposed for job strain and iso-strain; different categories of ERI) differ statistically from each other.

Figure 7.1 Cumulative survival probabilities (Kaplan-Maier) for incident type 2 diabetes by baseline job strain among men

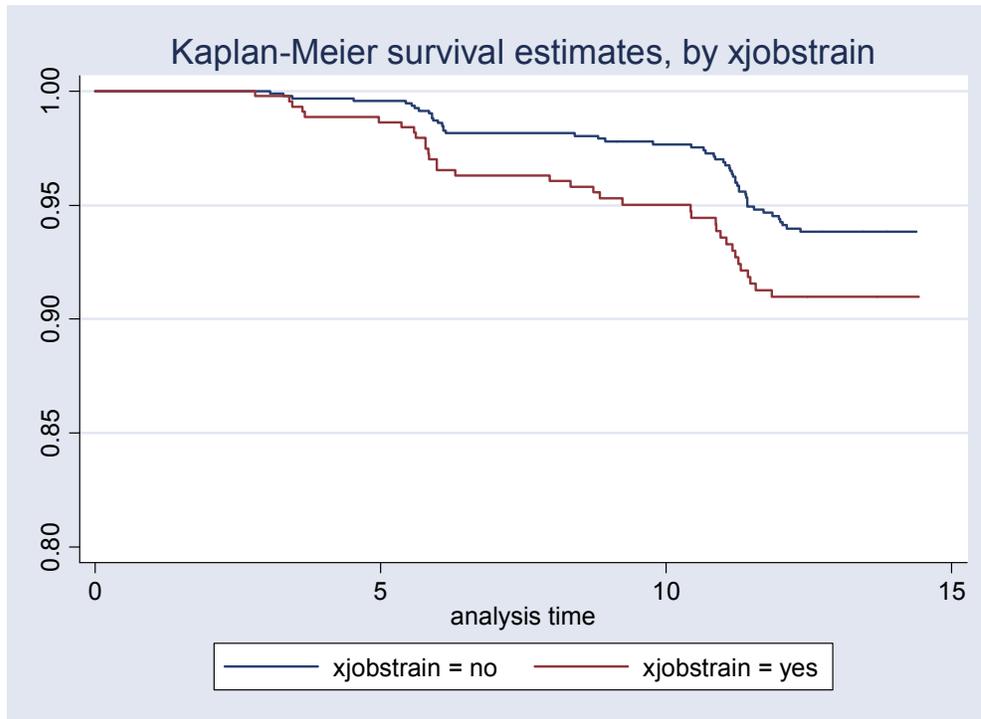


Log-rank $p=0.18$

Figure 7.1 shows that the survival probability for T2DM does not differ by baseline job strain among men. The log rank test p -value (0.18) confirms that the two graphs do not

significantly differ. This indicates that men with job strain did not differ in respect to T2DM risk compared to those with no job strain.

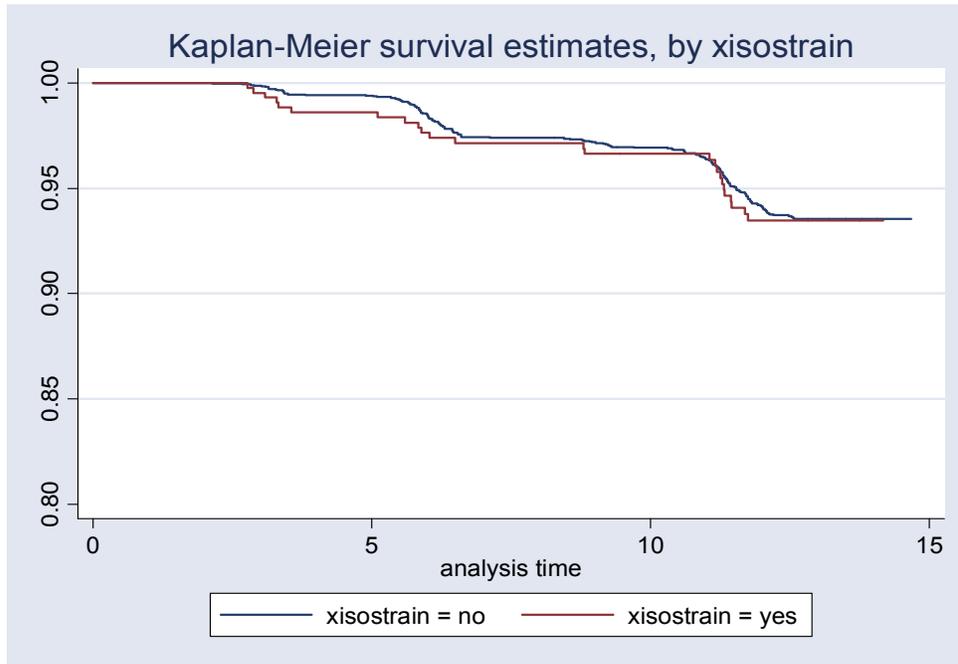
Figure 7.2 Cumulative survival probabilities (Kaplan-Maier) for incident type 2 diabetes by baseline job strain among women



Log-rank test $p=0.040$

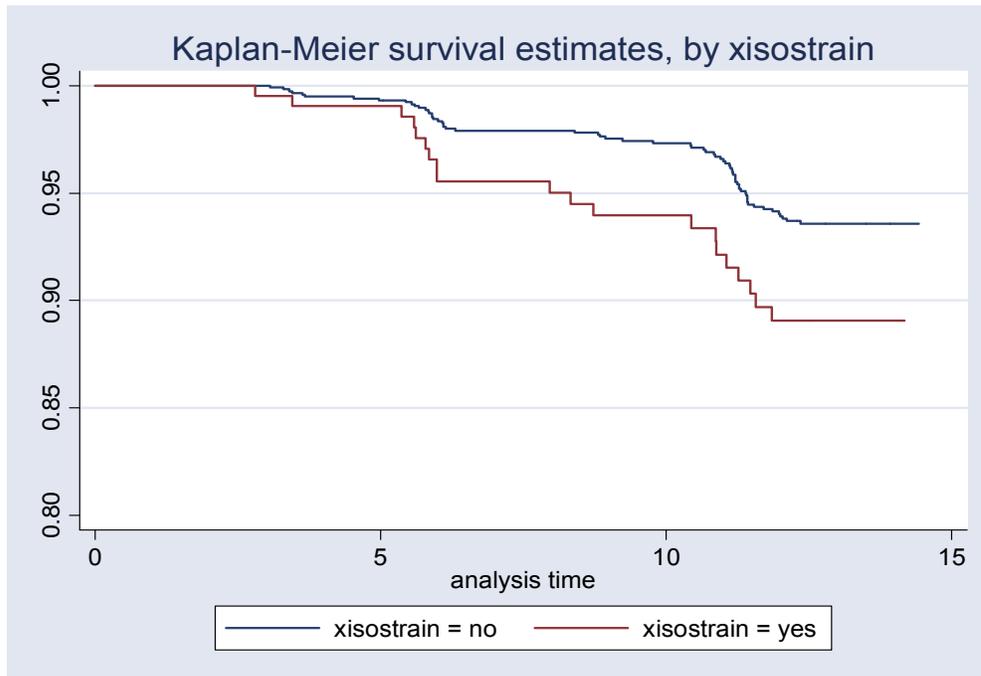
The picture was different among women (figure 7.2) with the curve (survival probability) for those with job strain being lower than in those with no baseline job strain. This was confirmed by the log-rank test for the difference in survival probabilities between those with and without job strain ($p=0.040$) indicating that the rate of T2DM differed by baseline job strain among women during follow-up.

Figure 7.3 Cumulative survival probabilities (Kaplan-Maier) for incident type 2 diabetes by baseline iso-strain among men



Log-rank test $p=0.86$

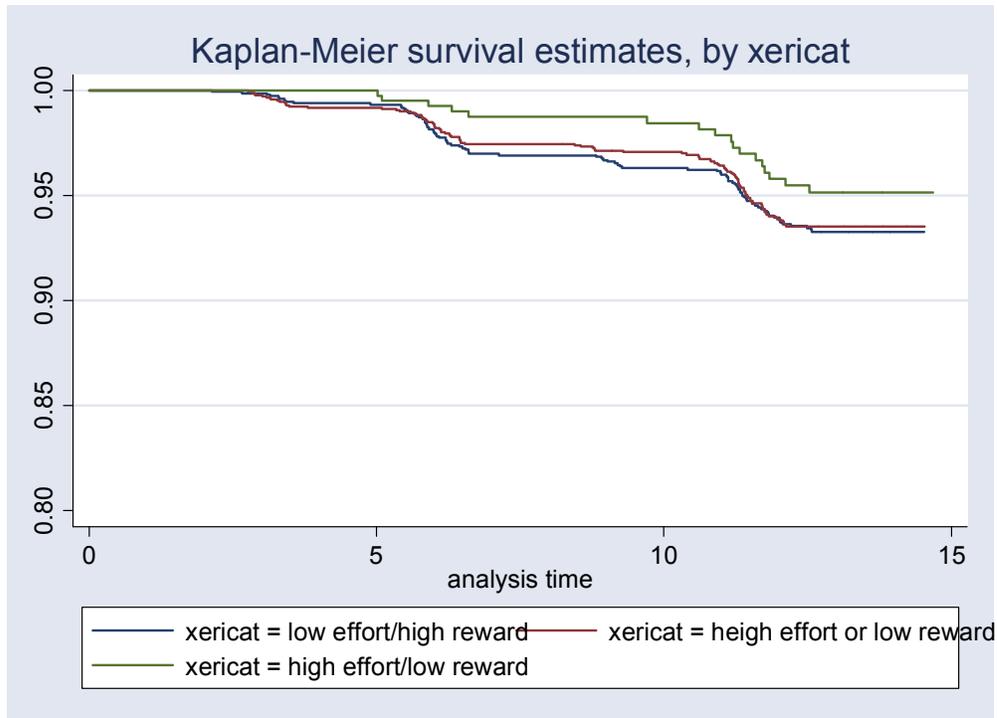
Figure 7.4 Cumulative survival probabilities (Kaplan-Maier) for incident type 2 diabetes by baseline iso-strain among women



Log-rank test $p=0.017$

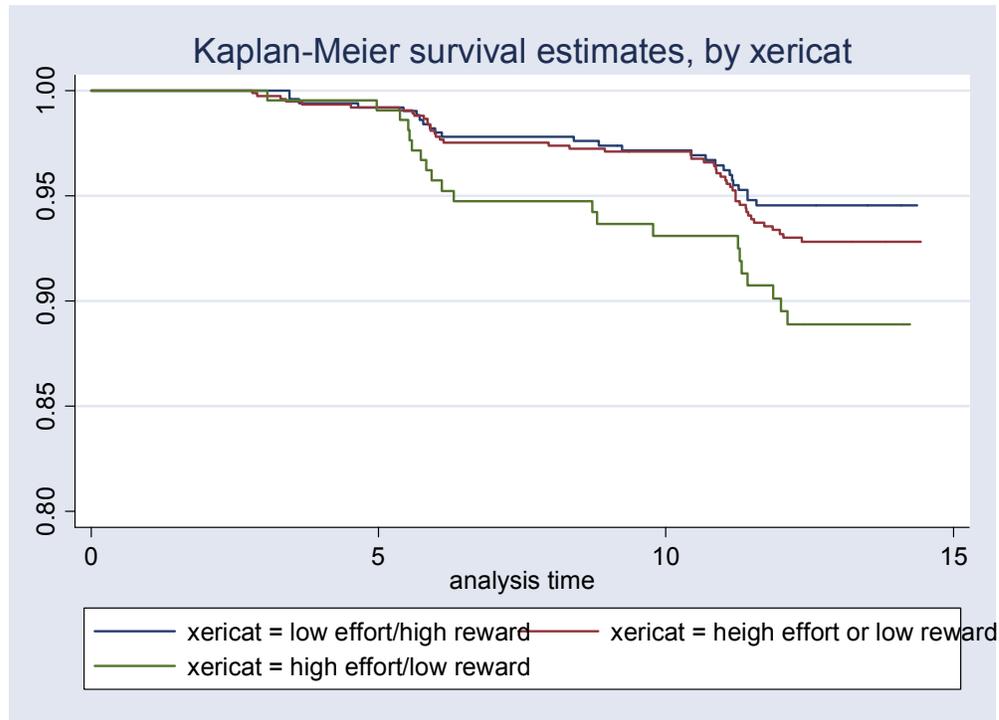
Similar to job strain, survival probabilities differed by iso-strain among women (figure 7.4) but not men (figure 7.3). The corresponding p-values testing differences in survival probabilities were 0.86 in men and 0.017 in women.

Figure 7.5 Cumulative survival probabilities (Kaplan-Maier) for incident type 2 diabetes by baseline effort-reward imbalance among men



Log-rank test p=0.34

Figure 7.6 Cumulative survival probabilities (Kaplan-Maier) for incident type 2 diabetes by baseline effort-reward imbalance among women



Log-rank test $p=0.035$

Figures 7.5 and 7.6 show survival probabilities by categories of ERI (low efforts AND high rewards; high efforts OR low rewards; high efforts AND low rewards). An unexpected finding of lower survival probability among men with low ERI (low effort AND high reward) was found (figure 7.5). This difference was not significant however (log rank test $p=0.34$). In figure 7.6, among women, the expected association of lower survival probabilities in the group of high ERI (high effort AND low reward) was found. These differences reached statistical significance as indicated by the log-rank test ($p=0.035$).

Overall, evidence from Kaplan-Meier curves from graphs 7.1-7.6 suggests that the psychosocial work stressors have an effect on incident T2DM among women but not among men. The next section shows results from multivariate adjusted Cox regression analysis on the effect of those psychosocial work stressors on incident T2DM.

7.6 Effect of psychosocial work stressors on incident T2DM adjusting for potential confounders

7.6.1 Adjusted association between psychosocial work stressors and incident T2DM

7.6.1.1 Demand/control/support model

Results from Cox regression analysis showing multivariate adjusted hazard ratios (adjusted for age employment grade, life events and height) for the effect of components of the demand/control/support model on incident T2DM among men and women after 15 years of follow-up in the WII study are presented in table 7.5.

Table 7.5 Multivariate adjusted Hazard Ratios (95% Confidence Intervals) for the effect of components of the demand/control/support model on incident type 2 diabetes among men and women after 15 years of follow-up in the Whitehall II study

	Model	Age-adjusted	Age+ employment grade	Age+ employment grade+ life events + height
	exposed cases/total exposed	HR (95% CI)	HR (95% CI)	HR (95% CI)
<i>Men</i>				
high job demands	104/2181	0.84 (0.64; 1.11)	0.90 (0.68; 1.19)	0.87 (0.65; 1.15)
low job control	80/1808	0.84 (0.63; 1.10)	0.70 (0.52; 0.95)	0.70 (0.52; 0.95)
low work social support	66/1280	0.98 (0.73; 1.31)	0.97 (0.72; 1.29)	0.93 (0.69; 1.25)
job strain	42/973	0.81 (0.58; 1.14)	0.77 (0.54; 1.08)	0.77 (0.55; 1.08)
iso-strain	25/467	1.09 (0.72; 1.66)	1.05 (0.69; 1.60)	1.01 (0.66; 1.54)
<i>Women</i>				
high job demands	40/737	1.07 (0.70; 1.63)	1.30 (0.84; 2.02)	1.29 (0.83; 2.01)
low job control	61/1108	1.09 (0.70; 1.71)	0.82 (0.51; 1.33)	0.82 (0.50; 1.33)
low work social support	31/556	1.14 (0.74; 1.77)	1.17 (0.75; 1.82)	1.16 (0.75; 1.80)
job strain	35/491	1.65 (1.07; 2.56)	1.54 (0.99; 2.39)	1.53 (0.98; 2.38)
iso-strain	20/230	2.07 (1.24; 3.43)	1.96 (1.17; 3.28)	1.95 (1.17; 3.27)

The association between job strain, iso-strain and their components and incident T2DM differed in men and women. In men, in the age-adjusted model (base model), there was no association between the job demands, job control, work social support, job strain and iso-strain variables and incident T2DM (table 7.5).

In women, in the age-adjusted model, high job demands, low job control and low work social support were not associated with risk of T2DM. The combination of high job demands and low job control (job strain) however was associated with a 65% higher risk of T2DM. Iso-strain, which combines job strain and low work social support, was associated with a 2-fold increase in T2DM risk after adjusting for age.

After adjusting for employment grade, the effect of job strain was attenuated to non-statistically significant but a ~50% higher risk remained comparing women with job strain to those with no job strain (Hazard Ratio 1.54: 95% confidence intervals 0.99; 2.39). The effect of iso-strain remained robust to adjustment for employment grade. Controlling for the effect of employment grade, women with iso-strain at baseline still had twice the risk for T2DM compared to women with no iso-strain (HR 1.96: 95% CI 1.17; 3.28). This effect also remained robust to adjustment for the degree upset by life events and height (HR 1.95: 95% CI 1.17; 3.27).

7.6.1.2 Effort-reward imbalance

The ERI components were assessed both as continuous and categorical measures in relation to incident T2DM. Results from Cox regression analysis showing multivariate adjusted hazard ratios for the effect of ERI and its components on incident T2DM among men and women are presented in table 7.6.

Table 7.6 Multivariate adjusted Hazard Ratios (95% Confidence Intervals) for the effect of components of the effort-reward-imbalance model on incident type 2 diabetes among men and women after 15 years of follow-up in the WII study

	Model	Age-adjusted	Age+ employment grade	Age+ employment grade+ life events + height
	exposed cases/total exposed	HR (95% CI)	HR (95% CI)	HR (95% CI)
<i>Men</i>				
efforts at work (continuous)*	n/a	0.88 (0.75; 1.03)	0.82 (0.70; 0.97)	0.83 (0.71; 0.98)
high effort at work	61/1367	0.87 (0.65; 1.17)	0.79 (0.58; 1.08)	0.80 (0.59; 1.10)
rewards at work (continuous)*	n/a	0.97 (0.84; 1.12)	0.96 (0.83; 1.11)	0.96 (0.83; 1.11)
low rewards at work	72/1501	0.93 (0.70; 1.24)	0.91 (0.68; 1.21)	0.91 (0.68; 1.21)
effort-reward imbalance (continuous)*	n/a	0.91 (0.77; 1.06)	0.86 (0.73; 1.01)	0.87 (0.74; 1.02)
effort-reward imbalance (categorical)				
<i>low efforts AND high rewards</i>	89/1605	reference	reference	reference
<i>high efforts OR low rewards</i>	100/1971	0.97 (0.73; 1.29)	0.91 (0.68; 1.21)	0.92 (0.68; 1.22)
<i>high efforts AND low rewards</i>	16/442	0.71 (0.42; 1.21)	0.62 (0.36; 1.07)	0.63 (0.37; 1.09)
<i>Women</i>				
efforts at work (continuous)*	n/a	1.16 (0.97; 1.39)	1.11 (0.92; 1.34)	1.11 (1.02; 1.35)
high effort at work	54/752	1.90 (1.24; 2.90)	1.74 (1.13; 2.67)	1.74 (1.13; 2.68)
reward at work (continuous)*	n/a	1.04 (0.85; 1.28)	1.03 (0.84; 1.26)	1.03 (0.85; 1.26)
low rewards at work	33/586	1.06 (0.69; 1.63)	1.01 (0.66; 1.55)	1.01 (0.66; 1.56)
effort-reward imbalance (continuous)*	n/a	1.11 (0.93; 1.32)	1.07 (0.89; 1.28)	1.07 (0.89; 1.28)
effort-reward imbalance (categorical)				
<i>low efforts AND high rewards</i>	24/553	reference		
<i>high efforts OR low rewards</i>	45/830	1.30 (0.79; 2.13)	1.18 (0.71; 1.96)	1.17 (0.71; 1.95)
<i>high efforts AND low rewards</i>	21/250	2.11 (1.17; 3.80)	1.83 (1.00; 3.34)	1.84 (1.01; 3.37)

*HR per 1 s.dev increase in exposure for continuous variables

Like the demand/control/support model, the effect of ERI differed by gender. In men, efforts at work had a protective effect on incident T2DM which reached statistical significance for the efforts scale (continuous variable). In women the opposite was observed, with increasing efforts at work being associated with an increased risk of T2DM, which reached statistical significance for the binary high efforts measure (90% higher risk comparing those with high efforts at work to those with low efforts in the age-adjusted model). Rewards at work were not associated with incident T2DM in either men or women. The protective effect of increasing efforts among men brought about an unexpected protective effect of the ERI scale on incident T2DM, which did not reach statistical significance however. In contrast, among women, increasing ERI scale had a harmful effect on incident T2DM. In the categorical measure of ERI (low efforts/high rewards; either high efforts or low rewards; high efforts/low rewards), the category 'high efforts/low rewards' was associated with a 2-fold higher risk of T2DM compared to the low efforts/high rewards group (reference) (HR 2.11: 1.17; 3.80).

Adjusting for employment grade increased the protective effect of efforts and ERI among men. Only the effect of the effort scale reached statistical significance however.

Adjusting for employment grade reduced the harmful effect of efforts and ERI among women. The harmful effect of being in the 'high efforts/low rewards' group among women, was reduced after adjustment for employment grade but remained statistical significant (HR 1.83: 1.00; 3.34). Further adjustment for the degree upset by life events and height did not alter these hazard ratios any further.

7.7 Effect modifications in the association between psychosocial work stressors and T2DM

Evidence for modification of the effect of psychosocial work stressors on incident T2DM by gender, age, employment grade and body weight status is presented in table 7.7.

Results on effect modifications by these factors are also presented separately for men and women in tables 7.8 and 7.9. The reason for this analysis was to exclude the possibility

that the interaction between work stress and the above factors was not due to the difference in the proportion of men and women in the strata of these factors. The analysis in tables 7.8 and 7.9 was performed only for iso-strain due to its stronger effect on incident T2DM.

Table 7.7 Hazard Ratios (95% Confidence Intervals)* for the effect of work stressors on incident type 2 diabetes stratified by gender, age, employment grade and body weight status

	exposed cases/total exposed	HR (95% CI)		p for interaction	
		Men	Women		
job strain	43/987	0.82 (0.59; 1.15)	35/512	1.59 (1.03; 2.45)	0.019
iso-strain	25/475	1.07 (0.71; 1.63)	20/241	1.94 (1.07; 3.21)	0.083
high ERI (high efforts/low rewards)	17/454	0.73 (0.45; 1.21)	21/262	1.70 (1.05; 2.78)	0.007
		Younger (<50 years)		Older (≥50 years)	
job strain	37/872	1.03 (0.70; 1.50)	41/627	1.04 (0.73; 1.49)	0.99
iso-strain	20/436	1.16 (0.72; 1.86)	25/280	1.51 (0.98; 2.31)	0.44
high ERI (high efforts/low rewards)	16/416	0.91 (0.54; 1.52)	22/300	1.24 (0.79; 1.94)	0.37
		High/middle employment grade		Low employment grade	
job strain	61/1271	0.95 (0.71; 1.27)	17/228	1.53 (0.84; 2.79)	0.18
iso-strain	34/622	1.15 (0.80; 1.65)	11/94	2.61 (1.32; 5.13)	0.040
high ERI (high efforts/low rewards)	29/521	1.14 (0.78; 1.68)	8/194	0.66 (0.31; 1.42)	0.25
		Non-obese (BMI<30kg/m²)		Obese (BMI≥30kg/m²)	
job strain	49/1331	0.86 (0.62; 1.18)	28/164	1.40 (0.88; 2.24)	0.057
iso-strain	27/621	1.10 (0.73; 1.64)	17/92	1.54 (0.89; 2.67)	0.22
high ERI (high efforts/low rewards)	27/646	1.04 (0.70; 1.56)	11/69	1.13 (0.59; 2.14)	0.81

*age-adjusted model

Table 7.8 Hazard Ratios (95% Confidence Intervals)* for the effect of work stressors on incident type 2 diabetes stratified by age, employment grade and body weight status among men

exposed cases/total exposed	HR (95% CI)	exposed cases/total exposed	HR (95% CI)	
Younger (<51 years)		Older (≥51 years)		<i>p for interaction</i>
13/314	0.99 (0.55; 1.77)	12/161	1.16 (0.63; 2.11)	0.72
High/middle employment grade		Low employment grade		
22/444	1.02 (0.65; 1.58)	3/31	1.53 (0.42; 5.51)	0.45
Non-obese (BMI<30kg/m²)		Obese (BMI≥30kg/m²)		
17/419	0.95 (0.58; 1.57)	7/53	0.91 (0.40; 2.09)	0.86

*age-adjusted model

Table 7.9 Hazard Ratios (95% Confidence Intervals)* for the effect of work stressors on incident type 2 diabetes stratified by age, employment grade and body weight status among women

exposed cases/total exposed	HR (95% CI)	exposed cases/total exposed	HR (95% CI)	
Younger (<51 years)		Older (≥51 years)		<i>p for interaction</i>
7/122	1.70 (0.73; 3.96)	13/119	1.97 (1.06; 3.67)	0.79
High/middle employment grade		Low employment grade		
12/178	1.52 (0.80; 2.90)	8/63	3.32 (1.47; 7.47)	0.18
Non-obese (BMI<30kg/m²)		Obese (BMI≥30kg/m²)		
10/202	1.54 (0.77; 3.08)	10/39	2.81 (1.34; 5.93)	0.090

*age-adjusted model

7.7.1 Effect modification by gender and age

Evidence for an interaction between work stressors and gender was already presented in the Kaplan-Meier graphs in figures 7.1-7.6. This evidence for no effect in men and a harmful effect in women was also shown in the Cox regression analysis in tables 7.5 and 7.6. A statistical test for interaction using the likelihood ratio test confirmed this effect modification by gender (LRT for interaction: $p=0.019$ for job strain; $p=0.083$ for iso-strain; and $p=0.007$ for ERI) (table 7.7). This gender interaction is further investigated in the following section of this chapter and is discussed in detail in the discussion chapter (chapter 10). There was no evidence for an interaction between work stressors and age in their association with incident T2DM in either men or women.

7.7.2 Effect modification by employment grade

The interaction between employment grade and work stress depended on which of the work stressor variables was used. There was evidence for an interaction between iso-strain and employment grade in their association with incident T2DM ($p=0.040$). The effect of iso-strain was higher in low grade participants (HR 1.51: 0.98; 2.31) compared to high/middle grade participants (HR 1.16: 0.72; 1.86). The effect of job strain was also higher in the low compared to the high employment grade, but the interaction did not reach statistical significance ($p=0.18$). ERI did not interact with employment grade ($p=0.25$). A protective effect of high ERI observed in the low grade, should be interpreted with caution due to the small number of T2DM cases exposed to high ERI in that group ($N=8$).

In gender specific analysis, the effect of iso-strain on T2DM was higher in the low grade among both men and women. In low grade men, there was an effect of 50% higher risk of T2DM in those exposed to iso-strain. This effect did not reach statistical significance however 1.53 (0.42; 5.51). The effect of iso-strain among low grade women (HR 3.32: 1.47; 7.47) was also substantially elevated compared to the effect in the whole sample (HR 1.94: 1.07; 3.21). These findings should be interpreted with caution due to the very

small number of T2DM cases in the categories of employment grade (for example 3 T2DM cases among men in the low grade exposed to iso-strain).

The interaction between iso-strain and employment grade can be interpreted as social vulnerability in the association between work stressors and incident T2DM. The effect modification by employment grade shows that participants who are better off in terms of their current occupation are protected from the harmful effects of work stressors in terms of T2DM development. The current results cannot prove however that high grade employees are 'immune' to the 'toxic' effects of psychosocial work stressors, due to the small number of T2DM cases among participants of high employment grade.

7.7.3 Effect modification by body weight status

Effect modification by body weight status was assessed stratifying by obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$ vs. $\text{BMI} < 30 \text{ kg/m}^2$). The effect of job strain and iso-strain was higher among participants who were obese at baseline compared to the non-obese but the evidence for job strain was stronger ($p=0.057$). ERI did not interact with obesity.

Unlike employment grade, the effect modification by body weight status differed by gender. In men there was no interaction between iso-strain and obesity. In women there was some evidence for an interaction between iso-strain and baseline obesity (LRT $p=0.090$). The effect of iso-strain was almost double among obese women (10 T2DM cases: HR 2.81: 1.34; 5.93) compared to non-obese women (10 T2DM cases: HR 1.54: 0.77; 3.08).

Overall, there was a clear and consistent effect modification by gender. In addition, the effect of work stressors on risk of T2DM was modified by employment grade and body weight status. These results support the chapter's second hypothesis for an effect modification by gender, employment grade and body weight status, but not age.

The gender differences in effect are further investigated in the following section since they do not support the chapter's first hypothesis of an effect of work stressors on T2DM among both men and women in the WII study.

7.8 Sensitivity analysis: Further investigation of gender differences

Before establishing that the gender difference in the effect of psychosocial work stressors on incident T2DM is a valid observation, the following 3 hypotheses were investigated in sensitivity analysis:

1. *There is* an association between work stressors and T2DM in men but the current analysis fails to show this due to bias introduced in the results (type II error);
2. *There is no* association between work stressors and T2DM in women and the observed effect is due bias or residual confounding (type I error)
3. The observed interaction between work stressors and gender may be a result of an interaction between work stressors and *employment grade or obesity*, which are both associated with gender and were shown to interact with work stressors.

7.8.1 Investigation of the lack of effect among men (type II error)

For the current analysis, it may be that information bias caused error in the results by diluting the effect of work stressors on incident T2DM in men. Men may have misreported their working conditions leading to misclassification in the work stressor variables and introducing systematic error in the results. This however is unlikely as a potential explanation as the job strain, iso-strain and ERI models of work stress were found to be predictive of several health outcomes including heart disease (Bosma et al, 1998; Kuper et al, 2002; Chandola et al, 2008), obesity (Brunner et al, 2007) and the metabolic syndrome (Chandola et al, 2006) in men in the WII study. In addition, for outcome ascertainment, the majority of the incident T2DM cases were identified using an

oral glucose tolerance test following a standardized protocol. The self-reported cases would have affected the results if they had been misreported, but it is unlikely that such misreporting in self-reported diabetes took place and only in men.

Selection bias may have distorted the results in men. Between phases 1 and 3 of the WII study there was considerable drop out. If participants exposed to psychosocial work stressors were dropping out at a higher rate than participants not exposed, this could introduce bias in the results. Drop out was investigated in the methods chapter (chapter 4). Tables 4.7 and 4.8 show that, indeed, participants exposed to work stressors were more likely to drop out during follow-up in the WII. In order to investigate whether this selective drop out differed by gender prevalence of work stressors among participants lost to follow-up and those included in analysis was examined separately in men and women (table 7.10).

Table 7.10 Proportion of participants with work stress in those who were lost to follow-up or excluded from current analysis and those who were included in analysis at WII phase 3

	Men		Women	
	Lost to follow-up or excluded from analysis (N=2707) % (number)	Included in current analysis (N=4166) % (number)	Lost to follow-up or excluded from analysis (N=1618) % (number)	Included in current analysis (N=1729) % (number)
Job strain – phase 1	22.1 (597)	19.8 (822)*	25.1 (406)	24.3 (413)
Iso-strain – phase 1	10.8 (292)	8.8 (362)*	13.9 (222)	10.4 (175)*
ERI – phase 1	21.1 (489)	22.7 (853)	31.0 (399)	33.0 (475)

*p<0.05

Table 7.10 shows that selective drop out by exposure to work stressor did not differ by gender. Therefore it is unlikely that bias due to selective drop-out could provide an explanation for the gender differences.

7.8.2 Investigation of the validity of the effect among women (type I error)

7.8.2.1 Residual confounding

It may be that residual confounding operated after adjustment in the current analysis as the validity of the instrument assessing life events (a potential confounder) in the WII study is not known. However, the major confounders (age and SEP) were accurately measured in the WII study. Apart for the major confounders (tables 7.5 and 7.6) the following additional potential confounders were also accounted for: (i) the self-reported mental state of participants during the 2 weeks prior to questionnaire completion; and (ii) tensions caused by anticipation of departmental privatization among some civil service departments. Both factors were associated with both psychosocial stress and incident T2DM (results not shown) and thus were used in Cox regression analysis as potential confounders in addition to the models presented in tables 7.5 and 7.6.

Table 7.11 Multivariate adjusted Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after additional adjustment for two potential confounders among women

	Age-adjusted	Age+ employment grade+ upset by life events + height	+bad psychological state last 2 weeks	+departmental relocation	+both
No of cases/total	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
20/226	2.07 (1.24; 3.43)	1.95 (1.16; 3.26)	2.02 (1.20; 3.40)	1.98 (1.18; 3.30)	2.06 (1.22; 3.45)

Table 7.10 shows that additional adjustment for the psychological state of the participants during the 2 weeks prior to questionnaire completion, as well as additional adjustment for the effect of tensions caused by departmental privatization did not alter the harmful effect of iso-strain on risk of T2DM among women participants. Residual confounding does not therefore appear, from these results at least, as a potential explanation for the observed effect among women and hence the gender differences.

7.8.2.2 Bias

Information bias may explain part of the effect among women as obese participants at phase 3, who were at an increased risk of developing T2DM (chapter 6), reported more adverse work characteristics as a result of their body weight status rather than their actual experience at work. To investigate this, the analysis was repeated excluding morbidly obese participants (class II and III obesity). These are participants with a BMI $\geq 35\text{kg/m}^2$.

Table 7.12 Age-adjusted Hazard Ratios (95% Confidence Intervals) for the effect of job strain, iso-strain and effort-reward imbalance on incident type 2 diabetes after exclusion of morbidly obese participants among women

		WHOLE SAMPLE	EXCLUDING PARTICIPANTS WITH BMI $\geq 35\text{kg/m}^2$ (N=40 men, 76 women)
	exposed cases/total exposed	HR (95% CI)	HR (95% CI)
job strain	35/491	1.65 (1.07; 2.56)	1.26 (0.76; 2.07)
iso-strain	20/230	2.07 (1.24; 3.43)	1.58 (1.86; 2.89)
ERI			
<i>low efforts AND high rewards</i>	100/1971	reference	reference
<i>high efforts OR low rewards</i>	16/422	1.30 (0.79; 2.13)	1.15 (0.66; 2.00)
<i>high efforts AND low rewards</i>	89/1605	2.11 (1.17; 3.80)	2.27 (1.22; 4.24)

Table 7.12 shows that excluding participants with a BMI $\geq 35\text{kg/m}^2$ from analysis resulted in an attenuation of the effect of job strain among women from a hazard ratio of 1.65 to 1.26 and the effect of iso-strain from 2.07 to 1.58. The effect of high ERI remained unchanged however (HR=2.3 after exclusion of morbidly obese). There is therefore a suggestion that reverse causation may explain some of the effect of job strain and iso-strain. This is discussed in more detail in the discussion chapter (chapter 10).

7.8.3 Investigating the involvement of employment grade and obesity in the gender differences

The differential effect by gender may be due to interaction between another variable and work stressors rather than between gender and work stressors. This possibility was examined by performing analysis within strata of employment grade and body weight status and using the likelihood ratio test to statistically test the gender interaction within strata of these variables (high middle vs. low grade; non-obese vs. obese). Results are shown in table 7.13.

Table 7.13 Interaction between iso-strain and gender stratifying by employment grade and body weight status

	exposed cases/total exposed	HR (95% CI)	exposed cases/total exposed	HR (95% CI)
	High/middle employment grade		Low employment grade	
men	22/444	1.02 (0.65; 1.58)	3/31	1.53 (0.42; 5.51)
women	12/178	1.52 (0.80; 2.90)	8/63	3.32 (1.47; 7.47)
<i>p gender interaction</i>		0.027		0.35
	Non-obese (BMI<30kg/m²)		Obese (BMI≥30kg/m²)	
men	17/419	0.95 (0.58; 1.57)	7/53	0.79 (0.33; 1.87)
women	10/202	1.54 (0.77; 3.08)	10/39	2.81 (2.34; 5.93)
<i>p gender interaction</i>		0.092		0.021

The results from table 7.13 on gender interactions within strata of other variables do not provide good evidence due to the small number of T2DM cases within strata of the variables used (employment grade and body weight status). Overall, there was some evidence for a gender interaction within the high/middle employment grade (interaction

$p=0.027$), within the non-obese group (interaction $p=0.092$), and within the obese group (interaction $p=0.021$). In contrast no evidence for a gender interaction was observed among the low grade group.

7.9 Comparison to other studies

In the systematic review of the literature presented in chapter 2, five studies were identified that investigated the effect of psychosocial work stressors, based on the demand/control/support and ERI models, on T2DM. Among these, 1 paper was from the WII study (Kumari et al, 2004), with follow-up from phase 1 to phase 5. Unlike the current analysis, Kumari et al (2004) found a harmful effect of ERI on incident T2DM among men but not among women. As in the current analysis, no effect was observed between the individual components of the demand/control/support model and incident T2DM. Job strain and iso-strain were not assessed in that analysis. The reasons for the discrepancies between the two WII analyses are discussed in detail in the discussion chapter (sub-section 10.2.2.3).

In the only prospective study other than WII investigating this association, the Nurses' Health Study II, job strain was not associated with incident T2DM (Kroenke et al, 2006). Iso-strain and ERI were not assessed in that study. The discrepancy with the current results may be due to differences in the population under study. In the WII sample of civil servants working conditions differ widely between the 5766 different jobs assessed and thus the variation in exposure to work stressors is probably higher. A recent review on the role of psychosocial work stressors in heart disease concluded that studies recruiting from a single employment (i.e. Nurses Health studies) are likely to under-estimate the effects of work stressors on disease outcomes (Eller et al, 2009). In the Nurses' Health Study II, working overtime was associated with increased risk of T2DM, therefore, among that sample, overtime work may be a more important work stressor than job strain.

Consistent with the present findings, two Swedish case-control studies found that job strain was associated with higher odds of type 2 diabetes in women but not in men

(Agardh et al, 2003; Norberg et al, 2007). The research group from the Stockholm Diabetes Prevention Program (Agardh et al, 2003) presented prospective results from their study in the European Diabetes Epidemiology Group 2009 conference showing evidence on gender differences, with an effect of job strain on incident T2DM in women but not in men (van den Donk, 2009). These results were not yet published by the completion of the current thesis.

The magnitude of the effect of job strain was slightly higher in the 2 case-control studies (2-3 fold higher odds) compared to the current results (~60% higher risk). It is more likely that the case-control studies over-estimated the effect rather than vice versa, as case-control study designs are more prone to information bias than prospective studies. These two case-control studies did not assess iso-strain or ERI. Lastly, the Belstress study in Belgium showed a 2-fold higher odds of T2DM among women exposed to job strain in cross-sectional analysis (Leynen et al, 2003). An effect was again lacking among men. Iso-strain and ERI were not assessed.

There is no evidence in the literature on modification of the effect of work stressors on incident T2DM by SEP or obesity. Previous evidence from the WII study (Kivimaki et al, 2006) suggests that in participants who were obese at baseline exposure to work stressors was prospectively associated with weight gain, while in those who were lean at baseline work stressors were associated with weight loss. Given the strong association between weight gain and risk of T2DM, these results support the current findings of effect modification by obesity in the effect of work stressors on T2DM.

Overall, the current results are in agreement with results from other studies for gender differences in the association between psychosocial work stressors and T2DM, with a relatively strong effect among women, which remains robust to adjustments.

7.10 Summary and link to next chapter

This chapter investigated the effect of psychosocial work stressors on incident T2DM among men and women in the WII study. Based on the specific objectives, the current chapter identified that:

1. The first hypothesis of the current chapter, that work stressors increase the risk of T2DM among middle-aged men and women was partly supported by the results. Compared to women not exposed to work stressors, women with job strain had a 60% higher risk of T2DM and women with iso-strain and high ERI had twice the risk of T2DM after 15 years of follow-up. These harmful effects were not observed among men. The effects among women remained robust to adjustment for potential confounders (age, SEP, outside work stressors and height).
2. The effect of work stressors on incident T2DM was modified by gender, employment grade and body weight status, with the effect being higher among women, among participants in low employment grades and among obese participants (especially obese women).

The current chapter examined, for the first time, estimates for the effect of the three main psychosocial work stressors (job strain, iso-strain and ERI) on clinically ascertained incident T2DM. This was the first and main aim of the current project. The following chapter investigates the excess risk and population impact associated with exposure to work stressors in relation to incident T2DM. Due to the lack of association between work stressors on incident T2DM among men, the analysis in the next chapter was conducted only among women.

Chapter 8: Impact of psychosocial work stressors on incident type 2 diabetes among women

8.1 Introduction

The previous chapter examined the effect of psychosocial work stressors on incident T2DM among men and women in the WII study and showed that psychosocial work stressors are associated with a 1.5 to 2-fold higher risk of T2DM among women. In addition to the magnitude of effect, it is important to examine excess disease risk in absolute terms attributed to the exposure of interest, as well as the impact of the exposure on disease among the study population.

Attributable risk (excess risk) refers to the excess number of disease cases that could have been prevented in the exposed group if the exposure was not present. Population attributable risk (population impact) refers to the excess number of disease cases that could have been prevented in the whole population under study if the exposure was not present. Measures of population impact depend both on the magnitude of the effect of the exposure as well as the prevalence of the exposure in the study population. For example an exposure with a very high effect on a disease (i.e. asbestos on lung cancer) does not always have a high impact on that disease (for example asbestos exposure is relatively rare in the population). Attributable risk and population attributable risk can also be presented as fractions, that is the proportion of all cases among the exposed (attributable fraction) or in the whole study population (population attributable fraction) that may be attributed to the exposure, on the assumption of a causal association.

Type 2 diabetes is a preventable disease in the biggest majority of cases and thus measures of excess risk and impact for specific exposures could be very informative in terms of the benefit in preventing the disease if the exposure was to be eliminated. In the US, it was found that 91% of T2DM cases among middle-aged women were attributed to health behaviours, including low physical activity and unhealthy diet, as well as obesity

(Hu et al, 2001). Evidence on the impact of psychosocial work stressors on health outcomes is very limited. Only few studies in the literature investigated the impact of job strain on disease and none on T2DM. The estimated figures suggest that between 10-20% of disease cases among the populations of these studies were attributed to job strain (Nurminen & Karjalainen, 2001; LaMontagne et al, 2008).

8.2 Chapter aim, objectives and main hypotheses

Aim:

To investigate attributable risk and population attributable risk of psychosocial work stressors on incident type 2 diabetes among women

Objectives:

1. To assess the attributable risk and attributable fraction for job strain and iso-strain on incident T2DM.
2. To assess the population attributable risk and population attributable fraction for job strain and iso-strain on incident T2DM.
3. To assess the population attributable risk and population attributable fraction on incident T2DM for conventional behavioural and biological risk factors and compare them to psychosocial work stressors.
4. To assess the additional attributable risk on incident T2DM due to iso-strain in co-occurrence with conventional behavioural and biological risk factors

Main hypotheses:

1. The impact of job strain and iso-strain on incident T2DM in the WII study is between 10-20% based on previous evidence.

2. The impact of psychosocial work stressors on incident T2DM is lower than the impact of behavioural and biological risk factors
3. Psychosocial work stressors have an additional absolute risk on incident T2DM when they co-occur with traditional behavioural and biological risk factors.

8.3 Chapter methodology

8.3.1 Sample description

The sample of participants used in the current analysis was the same used in chapters 6 and 7. As an effect of work stressors was found only among women, so the analysis of the current chapter concentrates on Caucasian female civil servants with complete data on psychosocial work stressors and incident T2DM, who were free from diabetes at WII phase 3 (N=1729).

8.3.2 Variables used in current chapter

The variables used in the current chapter, together with the sub-section in which they were described in the methods section, are listed below:

8.3.2.1 Main exposures and outcome

- Job strain (4.2.2.2.1)
- Iso-strain (4.2.2.2.1)
- Incident T2DM (4.2.2.1)

8.3.2.2 Other variables

- Age (4.2.2.3.2)
- Employment grade (4.2.2.3.2)
- Dietary energy density (4.2.2.5.1.2)

- Physical activity (4.2.2.5.2)
- Alcohol consumption (4.2.2.5.3)
- Body Mass Index (4.2.2.6.1.1)
- Waist circumference (4.2.2.6.1.2)
- Triglycerides (4.2.2.6.1)
- HDL cholesterol (4.2.2.6.1)
- Systolic blood pressure (4.2.2.6.2)
- Metabolic syndrome (4.2.2.6.3)

In order to calculate measures of attributable risk continuous variables were dichotomised in the following way: low physical activity (≤ 7.5 MET-hrs/wk) (WHO, 2004); unhealthy diet (highest quintile of dietary energy density); unhealthy alcohol consumption (heavy consumption or abstinence); unhealthy behaviour (presence of at least one of low physical activity, unhealthy diet and unhealthy alcohol consumption); obesity ($\text{BMI} \geq 30$ kg/m²); central obesity (waist circumference > 88 cm); hypertriglyceridaemia (≥ 1.69); low HDL-cholesterol (≤ 1.29); hypertension ($\geq 140/90$).

8.3.3 Statistical analysis

Attributable risk and population attributable risk were calculated by first estimating the age-adjusted incidence rate of T2DM was among the whole sample of women, the exposed (exposed to work stressors) and the unexposed. The formulae for calculating the attributable risk, attributable fraction, population attributable risk, and population attributable fraction are given in the methods chapter 4, sub-section 4.3.6. The methodology for calculation of rates is also given in the methods chapter (sub-section 4.3.2.5).

The measures of absolute risk and impact mentioned above were calculated for both job strain and iso-strain as well as other behavioural and biological T2DM risk factors including: low physical activity; high dietary energy density; non-moderate alcohol

consumption; at least one unhealthy behaviour; obesity (BMI and waist); hypertension; hypertriglyceridaemia; low HDL-cholesterol; and the metabolic syndrome.

For calculation of attributable risk for psychosocial work stressors after co-occurrence with conventional risk factors the following variables were derived: (i) co-occurrence of at least one unhealthy behaviour with iso-strain; (ii) co-occurrence of obesity (BMI \geq 30) with iso-strain; (iii) co-occurrence of the metabolic syndrome with iso-strain. The excess risk associated with addition of iso-strain was calculated by subtracting the AF of the conventional risk factor (i.e. obesity) on incident T2DM from the AF of the conventional factor + iso-strain:

$$\text{Additional attributable risk for iso-strain} = \text{AF of conventional exposure+iso-strain} - \text{AF of conventional exposure}$$

8.4 Impact of psychosocial work stressors on risk o T2DM among women

8.4.1 Attributable risk of psychosocial work stressors on incident T2DM

Estimates of the excess risk attributed to exposure to job strain and iso-strain among women in the WII study were calculated assuming a direct causal association. The cause-effect association between psychosocial work stressors and T2DM is uncertain/speculative as it is based on few observational findings, with some null results, and no evidence from intervention studies. Due to this any results should be interpreted with caution.

Table 8.1 Attributable risk for job strain and iso-strain for type 2 diabetes among women in the WII study

	N (exposed cases/total exposed)	Rate in exposed (95% CI)	Rate in unexposed (95% CI)	Attributable risk (per 1000 py)	Attributable fraction
job strain	35/512	6.69 (4.81; 9.32)	4.32 (3.28; 5.71)	2.32	35%
iso-strain	20/241	8.17 (5.27; 12.67)	4.55 (3.57; 5.80)	3.62	44%

Table 8.1 shows that 2.3 T2DM cases per 1000 person-years among participants with job strain are attributed to exposure to job strain, assuming a causal association. This is the 35% of the total T2DM cases among those with job strain (attributable fraction). The corresponding estimates for iso-strain were 3.6 cases per 1000 person-years, corresponding to 44% of the cases among women with iso-strain. These figures suggest that, assuming a causal association, eliminating job strain would prevent 35% and eliminating iso-strain 44% of T2DM cases among women exposed to these psychosocial work stressors.

8.4.2 Population impact of psychosocial work stressors on incident T2DM

This sub-section presents findings on the population impact of exposure to job strain and iso-strain among women in the WII study. The estimates of population impact (population attributable risk) are on the whole sample of women in the analysis, including those not exposed to work stressors.

Table 8.2 Population impact (population attributable risk) for job strain and iso-strain on type 2 diabetes among women in the WII study

	N (exposed/total)	Rate in exposed+unexposed (95% CI)	Rate in unexposed (95% CI)	Population attributable risk (per 1000 py)	Population attributable fraction
job strain	85/1606	5.08 (4.14; 6.24)	4.32 (3.28; 5.71)	0.76	15%
iso-strain	85/1602	5.08 (4.14; 6.24)	4.55 (3.57; 5.80)	0.53	10%

Table 8.2 shows the population impact of work stressors on incident T2DM in the study population, given by the population attributable risk and the population attributable risk fraction. The results indicate that 0.8 T2DM cases per 1000 person-years among the whole sample of women are attributed to job strain, assuming a causal association. The proportion of all T2DM cases attributed to job strain was 15%. The PAF was higher for job strain than iso-strain (10%), unlike the higher AF for iso-strain (table 8.1). This is due to the higher prevalence of job strain in the population. Assuming a causal association,

eliminating job strain among the current population of women would prevent 15% of T2DM cases in this population, while eliminating iso-strain would prevent 10% of all T2DM cases.

8.4.3 Comparison of the population impact of psychosocial work stressors with the population impact of other conventional risk factors of T2DM

In order to assess the relative impact of exposure to psychosocial work stressors on incident T2DM, the estimates in table 8.2 are compared to estimates on the population impact of conventional risk factors. As in the case of work stressors, these impact estimates assume cause-effect associations

Table 8.3 Population impact (population attributable risk) for psychosocial work stressors and conventional risk factors on type 2 diabetes among women in the WII study

	N (exposed cases/total exposed)	Rate (95% CI) whole sample	Rate (95% CI) unexposed	PAR	PAF
job strain	35/512	5.08 (4.14; 6.24)	4.32 (3.28; 5.71)	0.76	15%
iso-strain	20/241	5.08 (4.14; 6.24)	4.55 (3.57; 5.80)	0.53	10%
low physical activity (<7.5 MET-hrs/wk)	18/328	5.08 (4.14; 6.24)	4.94 (3.93; 6.21)	0.14	3%
unhealthy diet (energy density Q5)	13/200	5.08 (4.14; 6.24)	4.84 (3.88; 6.04)	0.24	5%
unhealthy alcohol consumption (non-moderate)	37/522	5.08 (4.14; 6.24)	4.19 (3.22; 5.46)	0.89	17%
unhealthy behaviour (≥1)	52/842	5.08 (4.14; 6.24)	4.11 (3.02; 5.61)	0.98	19%
obesity (BMI≥30kg/m²)	36/243	5.08 (4.14; 6.24)	3.56 (2.74; 4.62)	1.52	30%
high waist circ. (>88)	35/221	5.08 (4.14; 6.24)	3.58 (2.76; 4.64)	1.50	30%
hypertension (≥140/90)	20/188	5.08 (4.14; 6.24)	4.43 (3.51; 5.58)	0.65	13%
hypertriglyceridaemia (≥1.69)	28/267	5.08 (4.14; 6.24)	4.08 (3.19; 5.22)	1.00	20%
low HDL-cholesterol (≤1.29)	29/273	5.08 (4.14; 6.24)	4.05 (3.16; 5.20)	1.03	20%
metabolic syndrome (ATP III definition)	28/157	5.08 (4.14; 6.24)	3.82 (2.99; 4.89)	1.26	25%

Table 8.3 shows the impact of job strain and iso-strain on incident T2DM in comparison to several behavioural and biological factors associated with incident T2DM in this study population (chapter 6). The impact of the psychosocial work stressors on incident T2DM was similar or higher than that of individual unhealthy behaviours (low physical activity, unhealthy diet, non-moderate alcohol consumption) but lower than that of biological risk factors.

It should be noted however that the assessment of health behaviours is prone to measurement error. Dietary assessment, in particular, is prone to considerable misreporting of intake leading to inaccurate estimates about diet-disease associations. Similar considerations apply to alcohol consumption and physical activity. Adjusting for energy intake misreporting (EI:TEE) in the current analysis does not completely resolve this phenomenon. Given this, it is expected that true impact of health behaviours is higher than that estimated in the current analysis.

Obesity had the greatest impact (30% of T2DM cases attributed to $BMI \geq 30 \text{kg/m}^2$) from the assessed risk factors on incident T2DM. Biological risk factors had a larger impact (20-25% of cases) on incident T2DM than the psychosocial work stressors, with the exception of hypertension (PAF=13%).

8.4.4 Attributable risk of psychosocial work stressors on incident T2DM when these co-occur with conventional risk factors

As T2DM is a multifactorial disease with several factors associated with its incidence, the attributable risk associated with work stressors when these co-occur with other risk factors was calculated and is presented in table 8.4.

Table 8.4 Attributable fraction for iso-strain during co-occurrence with conventional risk factors for type 2 diabetes among women in the WHI study

	N (exposed cases/total exposed)	Rate (95% CI) exposed	Rate (95% CI) unexposed	AR	AF	AF for iso-strain
iso-strain	20/241	8.17 (5.27; 12.67)	4.55 (3.57; 5.80)	3.62	44%	n/a
unhealthy behaviour (≥1)	52/842	6.25 (4.77; 7.21)	4.11 (3.02; 5.61)	2.14	34%	n/a
obesity (BMI≥30kg/m²)	36/243	15.49 (11.18; 21.48)	3.56 (2.74; 4.62)	11.93	77%	n/a
metabolic syndrome (ATP III definition)	28/157	20.64 (14.25; 29.89)	3.82 (2.99; 4.89)	16.82	81%	n/a
unhealthy behaviours + iso-strain	10/116	9.04 (4.86; 16.80)	4.65 (3.65; 5.92)	4.39	49%	15%
obesity + iso-strain	10/39	29.70 (15.98; 55.20)	4.58 (3.65; 5.75)	25.12	85%	8%
metabolic syndrome + iso-strain	6/23	31.49 (14.15; 70.10)	4.63 (3.64; 5.90)	26.86	85%	4%

Table 8.4 shows the additional excess risk associated with iso-strain after its co-occurrence with conventional behavioural and biological risk factors among the whole sample of women. The unhealthy behaviour variable summarizes the excess risk of all three unhealthy behaviours associated with incident T2DM (34% of T2DM cases among those with at least one unhealthy behaviour attributed to this behaviours). Obesity was the single risk factor with the greater excess risk in relation to incident T2DM (77% of T2DM cases among the obese attributed to obesity). The metabolic syndrome summarizes the overall excess risk of cardiometabolic risk factors and had the greater overall excess risk (81% of T2DM cases among those with the metabolic syndrome attributed to the metabolic syndrome).

Addition of iso-strain on the unhealthy behaviour measure increased the excess risk from 34% to 49%. There was therefore a 15% additional excess risk when iso-strain co-occurred with at least one health behaviour. This means that eliminating iso-strain could benefit in reducing the incidence of T2DM in addition to elimination of unhealthy behaviours in this population. For obesity and the metabolic syndrome the case was different, with only a minor increase in excess risk after addition of iso-strain (8% in the

case of obesity and 4% in the case of the metabolic syndrome). This indicates that if obesity or the metabolic syndrome were eliminated, the additional elimination of work stressors would provide only a small benefit in the incidence of T2DM in this population.

8.4.5 Sensitivity analysis: Attributable risk and impact among low grade and obese women

As both the prevalence of work stressors and the magnitude of the effect of these stressors on incident T2DM are higher among obese and low grade participants compared to the whole population (chapter 7), it is expected that impact will be higher among these participants. In order to examine this, the analyses presented in tables 8.1 and 8.2 for the whole sample of women, were repeated among obese women and women in the low employment grades.

Table 8.5 Attributable risk for job strain and iso-strain for type 2 diabetes among obese and low grade women in the WII study

	N (exposed cases/total exposed)	Rate in exposed (95% CI)	Rate in unexposed (95% CI)	Attributable risk (per 1000 py)	Attributable fraction
OBESE					
job strain	16/69	25.23 (15.46; 41.19)	10.88 (6.86; 17.28)	14.35	57%
iso-strain	10/39	29.70 (15.98; 55.20)	12.27 (8.23; 18.31)	17.43	59%
LOW GRADE					
job strain	12/169	7.93 (4.50; 13.96)	5.22 (3.33; 8.19)	2.71	34%
iso-strain	8/63	14.88 (7.44; 29.75)	4.99 (3.32; 7.51)	9.89	66%

Table 8.5 shows attributable risk for job strain and iso-strain in relation to incident T2DM among obese and low grade women. Among obese women, the attributable risk for job strain and iso-strain was higher, consistent with the greater effect of work stressors on incident T2DM in this group of women (Chapter 7, table 7.9). The proportion of T2DM

cases attributed to job strain and iso-strain among those exposed, were 57% and 59% respectively, assuming a causal association.

Among women in the low employment grade, the attributable risk for job strain (34% of all cases among exposed) was similar to that observed among the whole sample of women (35% of cases). For iso-strain however the corresponding proportion was 66%, a proportion much higher than that observed among the whole sample of women (44% of cases). The differences between job strain and iso-strain among low grade women are due to the much higher effect of iso-strain compared to job strain on incident T2DM among the low-grade women. This finding suggests that work social support is of major importance among those in low grades of employment. The results among obese women and low grade women should be interpreted with caution due to the small number of participants within these sub-groups.

Table 8.6 Population impact (population attributable risk) for job strain and iso-strain on type 2 diabetes among obese and low grade women in the WII study

	N (exposed/total)	Rate in exposed+unexposed (95% CI)	Rate in unexposed (95% CI)	Population attributable risk (per 1000 py)	Population attributable fraction
OBESE					
job strain	34/237	15.49 (11.18; 21.48)	10.88 (6.86; 17.28)	4.61	30%
iso-strain	34/237	15.49 (11.18; 21.48)	12.27 (8.23; 18.31)	3.22	21%
LOW GRADE					
job strain	78/1320	6.25 (4.46; 8.75)	5.22 (3.33; 8.19)	1.03	17%
iso-strain	78/1317	6.25 (4.46; 8.75)	4.99 (3.32; 7.51)	1.26	20%

Table 8.6 shows the population impact for T2DM attributed to exposure to job strain and iso-strain among obese and low grade women. Among obese women, exposure to job strain and iso-strain was responsible for the 30% and 21% respectively of total T2DM cases, assuming a causal association. Among women in the low-grade, the proportion of

T2DM cases attributed to job strain was 17% and the corresponding proportion for iso-strain was 20%. Unlike the whole sample of women, the impact of iso-strain was higher than that of job strain among the low grade women. This is due to the much higher effect of iso-strain than job strain among the low grade women. As already mentioned PAF depends on both the magnitude of effect and the prevalence of the exposure in the population.

8.5 Comparison to other studies

As mentioned in this chapter's introduction, there are only few studies that looked at the impact of psychosocial work stressors on disease outcomes. A paper from Finland estimated the PAF for job strain in relation to CHD mortality using a prevalence of 19% for men and 23% for women and a relative risk of 2.00 (Nurminen & Karjalainen, 2001). These are similar to the prevalence for job strain (24% and 32% for men and women respectively) and iso-strain (12% and 15% for men and women respectively) and relative risk of 1.65 (job strain) and 2.07 (iso-strain) for T2DM observed in the current analysis (chapter 7, table 7.5). Nurminen & Karjalainen (2001) calculated PAF for job strain to be 16% for men and 19% for women. This is similar to the PAF of 15% estimated for job strain among women in current analysis

In a paper by Steenland et al (2003) estimates on the effect of job control on CHD from several studies were used for calculating the PAF for job control in relation to CHD mortality. The meta-analyzed effect of job control on CHD was 1.38. Using this figure the authors of the paper calculated the PAF for job control in relation to CHD mortality to be 7%, in a population with a prevalence of job control of 20%. The authors state in their paper that they intentionally ignored job strain and concentrated on job control due to lack of evidence linking job demands to CHD. This is however a limitation of that analysis since most studies that have investigated psychosocial work stressors in relation to cardiometabolic disease, including the current project, provide evidence supporting that job strain has a stronger effect on disease risk than job control alone.

Two studies assessed the PAF of job strain in relation to depression. In a Finish study by (Nurminen & Karjalainen, 2001) it was estimated that 15% of deaths related to depression among men and 10% among women were attributable to job strain. In another study (LaMontagne et al, 2008) the effect of job strain on depression from a meta-analysis was estimated to be a relative risk of 1.82 and the prevalence of job strain to be 19% in men and 26% in women. The PAF for job strain in relation to depression was calculated to be 13% for men and 17% for women.

A recent WHO global quantitative risk assessment initiative (Eijkemans & Takala, 2005) investigated the population impact on morbidity and mortality for selected occupational risk factors but these did not include psychosocial work stressors.

8.6 Summary and link to next chapter

This chapter investigated the attributable risk and population attributable risk for psychosocial work stressors in relation to incident T2DM among women in the WII study. Based on the specific objectives, the current chapter identified that:

1. The attributable risk of psychosocial work stressors on incident T2DM was 2.3 and 3.6 cases per 1000 person-years for job strain and iso-strain respectively. Among participants exposed to job strain 35% of all T2DM cases were attributed to this exposure. The corresponding estimate for iso-strain was 44%.
2. The estimated population impact of job strain was 15% of all T2DM cases and that of iso-strain 10% of all T2DM cases in the current population of middle-aged Caucasian women in the WII study. 10-15% of all T2DM cases among women in the WII study are estimated to be attributed to psychosocial work stressors. These estimates are similar to those observed in other studies looking at the population impact of work stressors on heart disease and depression.

3. The population impact of psychosocial work stressors was similar to the population impact of individual behavioural factors (unhealthy diet, low physical activity, unhealthy alcohol consumption) and lower than the population impact of biological risk factors, especially general and central obesity and the metabolic syndrome.

4. Psychosocial work stressors have an additional attributable risk on incident T2DM when they co-occur with behavioural risk factors but the corresponding attributable risk in co-occurrence with biological risk factors is small.

This chapter calculated, for the first time, estimates for the impact of psychosocial work stressors on T2DM, which was the second aim of the current project. The following chapter will investigate the pathways through which psychosocial work stressors affect the incidence of T2DM.

Chapter 9: Pathways between psychosocial work stressors and type 2 diabetes among women

9.1 Introduction

In previous chapters the effect of psychosocial work stressors on incident T2DM was assessed after adjusting for potential confounders (Chapter 7) and the risk factors for T2DM in the WII study were identified (Chapter 6). This chapter investigates the extent to which behavioural and biological factors, identified as T2DM risk factors in chapter 6, may mediate the association between psychosocial stressors and T2DM incidence. The hypothetical pathways linking psychosocial work stressors to T2DM were discussed in detail in chapters 1 and 2. Briefly, the pathways can be generally divided into two types; direct and indirect. Indirect pathways operate through health behaviours. Direct pathways, as the name suggests, refer to the ways in which exposure to psychosocial stressors may directly alter the physiology of the body in a way to increase disease risk. The main proposed pathogenic mediators in the response to psychosocial stressors are increased accumulation of body fat, elevated blood pressure and blood lipids, as well as chronic activation of innate immunity (Brunner, 1997; McEwan, 1998; Brotman et al, 2008).

Evidence among participants of the WII study (WII Psychobiology sub-study) shows that experimental exposure to acute psychosocial stressors increases systolic blood pressure (Steptoe & Marmot, 2006) and the production of inflammatory markers such as CRP, IL-6 (Steptoe et al, 2002), fibrinogen, vWf and factor VII (Steptoe & Marmot, 2006). Exposure to chronic psychosocial stressors is very different however from exposure to acute experimental stressors. Empirical evidence on the association between chronic exposure to psychosocial work stressors and behavioural and biological risk factors was described in chapter 2 of the thesis (section 2.3).

The literature review showed that there was some evidence that psychosocial work stressors are associated with unhealthier behaviours (mainly smoking and lack of physical activity) and elevations in cardiometabolic risk factors (especially obesity and blood lipids) and inflammatory markers (especially fibrinogen). In the WII study, psychosocial work stressors were not associated with health behaviours in a recent analysis (Lallukka et al, 2008), but low job control and social isolation have been linked cross-sectionally with raised plasma fibrinogen level (Brunner et al, 1996; Steptoe et al, 2003) and delayed systolic blood pressure recovery (Steptoe & Marmot, 2006). Also, depression has been recently linked to increased CRP levels among a sample of 6126 men and women in the Czech Republic (Pikhart et al, 2009).

Given the observed association between unhealthy behaviours and cardiometabolic/inflammatory factors and T2DM incidence in the WII study (chapter 6), it is likely that some of the effect of work stressors on incident T2DM in the WII study is mediated by behavioural and biological risk factors. Among biological risk factors, obesity stands out as the most important potential mediator of the effect of psychosocial work stressors on T2DM due to evidence for an association between work stressors and obesity in the WII study (Kivimaki et al, 2006; Brunner et al, 2007) and the strong effect of obesity on T2DM (chapter 6, table 6.9).

This results chapter addresses the issue of mediation in the work stressors-T2DM association by first investigating the association between iso-strain and potential behavioural and biological mediators, followed by a calculation of the reduction in the effect of iso-strain on incident T2DM after adjustment for these potential mediators. This analysis is only presented for women as no effect of work stressors on incident T2DM was observed among men.

9.2 Chapter aim, objectives and main hypotheses

Aim:

To examine the proposed direct and indirect pathways linking psychosocial work stressors to T2DM risk in the Whitehall II study.

Objectives:

1. To assess unadjusted and adjusted cross-sectional associations between iso-strain and behavioural and biological T2DM risk factors among women at phase 3 of the Whitehall II study.
2. To assess the mediating effect of individual and grouped behavioural and biological risk factors in the iso-strain-incident T2DM association among women.
3. To examine the overlap between direct and indirect pathways linking iso-strain to incident T2DM

Main hypotheses:

1. Participants exposed to iso-strain have unhealthier behaviours and higher levels of biological T2DM risk factors.
2. Health behaviours (indirect pathway) and cardiometabolic and inflammatory factors (direct pathway) partly mediate the association between iso-strain and T2DM risk among women. Obesity is the most important mediator of the effect of iso-strain on T2DM risk.
3. The indirect pathway partly exerts its mediating effect through changes in biological factors (obesity, blood pressure, blood lipids, inflammation).

9.3 Chapter methodology

9.3.1 Sample description

Chapter 7 revealed that exposure to psychosocial work stressors increased the risk of T2DM among women. The current chapter investigates the pathways between

psychosocial work stressors and T2DM only among the sample of women who were included in the multivariate adjusted analysis in chapter 7. These are women who had valid data on incident diabetes, iso-strain, employment grade, life events and height (N=1550). These are the variables included in the final model adjusting for potential confounders in chapter 7.

9.3.2 Variables used in current chapter

For the current chapter, all mediations were examined with iso-strain as the work stressor of interest. Iso-strain was chosen as it showed a strong effect on incident T2DM and its effect was modified by employment grade and obesity. Appendix 5 summarizes the factors predicting the incidence of T2DM in the WII study. The behavioural and biological factors that predicted incidence of T2DM among women are those selected as potential mediators for the current chapter. All the variables used in the current chapter, together with the sub-section in which they were described in the methods section, are listed below:

9.3.2.1 Main exposures and outcome

- Iso-strain (4.2.2.2.1)
- Incident T2DM (4.2.2.1)

9.3.2.2 Potential confounders and mediators

- Age (4.2.2.3.2)
- Employment grade (4.2.2.3.2)
- Life events (4.2.2.4.2)
- Height (4.2.2.6.1.1)
- Dietary energy density (4.2.2.5.1.2)
- Energy Intake:Total Energy Expenditure (4.2.2.5.1.5)
- Physical activity (4.2.2.5.2)

- Alcohol consumption (4.2.2.5.3)
- Smoking status (4.2.2.5.4)
- Body Mass Index (4.2.2.6.1.1)
- Waist circumference (4.2.2.6.1.2)
- Waist-hip ratio (4.2.2.6.1.2)
- Waist-height ratio (4.2.2.6.1.2)
- Triglycerides (4.2.2.6.1)
- HDL cholesterol (4.2.2.6.1)
- Systolic blood pressure (4.2.2.6.2)
- Fibrinogen (4.2.2.6.3.1)
- C-reactive protein (4.2.2.6.3.2)
- Interleukin-6 (4.2.2.6.3.3)
- von Willebrand factor (4.2.2.6.3.4)
- Factor VII (4.2.2.6.3.5)
- Metabolic syndrome (4.2.2.6.3)

Additional variables were used for summarising behavioural and biological factors. Health behaviours were dichotomised according to gender in the following way: low physical activity (≤ 7.5 MET-hrs/wk for men and women); (www.who.int/dietphysicalactivity); unhealthy diet (highest quintile of dietary energy density); unhealthy alcohol consumption (heavy consumption or abstinence for women only). In order to summarise all health behaviours, an unhealthy behaviour score was derived based on the number of unhealthy behaviours for each female participant (low physical activity; unhealthy diet; unhealthy alcohol consumption). Participants scored 1 if they were unhealthy in 1 of 3 health behaviours; 2 when they were unhealthy in any 2 health behaviours; and 3 if they were unhealthy in all 3 health behaviours.

9.3.3 Statistical analysis

In order to investigate the mediating effect of individual behavioural and biological risk factors in the work stressor-incident T2DM association, each factor was added

individually in the final multivariate adjusted Cox regression model of chapter 7, containing age, employment grade, life events and height as potential confounders:

Model adjusted for confounders

$$h(t) = h_0(t) * \exp(\beta_1 \text{work stressor} + \beta_2 \text{age} + \beta_3 \text{employment grade} + \beta_4 \text{life events} + \beta_5 \text{height})$$

Model adjusted for confounders + potential mediator

$$h(t) = h_0(t) * \exp(\beta_1 \text{work stressor} + \beta_2 \text{age} + \beta_3 \text{employment grade} + \beta_4 \text{life events} + \beta_5 \text{height} + \beta_6 \text{BMI})$$

This procedure was followed for all potential mediators individually, as well as for the unhealthy behaviour score and the metabolic syndrome. Based on their effect as mediators, variables were further grouped and included simultaneously in the adjusted model in the following way:

$$h(t) = h_0(t) * \exp(\beta_1 \text{work stressor} + \beta_2 \text{age} + \beta_3 \text{employment grade} + \beta_4 \text{life events} + \beta_5 \text{height} + \beta_6 \text{BMI} + \beta_7 \text{HDL} + \beta_8 \text{fibrinogen} + \beta_9 \text{CRP} + \beta_{10} \text{IL-6} + \beta_{11} \text{vWf} + \beta_{12} \text{factorVII})$$

Potential mediators were included subsequently into the model in this way until no further mediation of effect was observed. The formula for calculating percent reduction in risk is given in the methods chapter, section 4.4 (Rothman, 1998; Chandola et al, 2008). Estimates for reduction of risk (mediation) are presented only if the effect after inclusion of the mediator was smaller than the initial adjusted effect (i.e. only if there was a reduction in risk after inclusion of the mediators). The hypothesized pathways linking psychosocial work stressors to T2DM are shown in figure 2.1 in chapter 2.

9.4 Elucidation of pathways between psychosocial work stressors and T2DM

9.4.1 Association between psychosocial work stressors and potential mediators

In order to help identify potential mediators in the iso-strain-incident T2DM association, associations were examined between iso-strain and behavioural and biological factors found to predict incident T2DM among women in chapter 6.

Table 9.1 Cross-sectional associations between iso-strain and factors associated with incident type 2 diabetes at phase 3 of the WHI study among women

	No iso-strain (N=1316)	Iso-strain (N=234)	<i>p</i> -value for difference
Alcohol consumption (%)			
no	26.5 (360)	24.9 (60)	
moderate	69.4 (945)	71.8 (173)	
heavy	4.1 (56)	3.3 (8)	0.71
Physical activity (mean)	3.10 (0.08)	2.99 (0.19)	0.62
Dietary energy density (mean)	1.03 (0.01)	1.04 (0.02)	0.54
Unhealthy behaviour score	0.61 (0.02)	0.64 (0.05)	0.56
Body Mass Index (mean)	25.8 (0.11)	26.2 (0.31)	0.16
Waist circumference (mean)	78.0 (0.31)	78.6 (0.79)	0.44
Waist-hip-ratio (mean)	0.80 (0.002)	0.80 (0.005)	0.98
Waist-height ratio (mean)	0.48 (0.002)	0.48 (0.005)	0.47
Triglycerides (mean)	1.19 (0.02)	1.19 (0.04)	0.92
HDL-cholesterol (mean)	1.68 (0.01)	1.69 (0.03)	0.70
Systolic blood pressure (mean)	117.5 (0.37)	118.4 (0.85)	0.34
Fibrinogen (mean)	2.57 (0.02)	2.59 (0.04)	0.56
C-reactive protein (mean)	2.07 (0.09)	2.51 (0.46)	0.11
Interleukin-6 (mean)	2.17 (0.07)	2.15 (0.13)	0.92
von Willebrand factor (mean)	107.0 (1.16)	107.2 (2.58)	0.95
Factor VII (mean)	93.2 (0.82)	96.7 (2.37)	0.11
Metabolic syndrome (%)	9.8 (132)	9.5 (123)	0.88

Table 9.1 shows cross-sectional associations between iso-strain and behavioural and biological T2DM risk factors among women. There is no evidence for an association

between any of the risk factors with iso-strain among the whole sample of women. Women with iso-strain do, however, have a higher unhealthy diet score, mean BMI and higher mean levels of the inflammatory markers CRP and factor VII. The associations between iso-strain and T2DM risk factors were also assessed using linear and logistic regression analysis adjusting for age and employment grade (results not shown) and the results were identical to those presented in table 9.1.

In spite of the fact that the effect of work stressors on incident T2DM was only observed among women (apart from a non-significant effect among low grade men), associations between iso-strain and incident T2DM risk factors were assessed among men as well. The risk factors assessed among men differ from those among women as the determinants of T2DM differed by gender in the WII study (chapter 6). These results can be found in appendix 6.

9.4.2 Mediating effect of different risk factors in the association between psychosocial work stressors and T2DM

9.4.2.1 Indirect effect through health behaviours

As described briefly in the current chapter's introduction and in more detail in the thesis introduction chapter, health behaviours could potentially mediate the effect of work stressors on incident T2DM due to their association with both work stressors and incident T2DM. Even though evidence for the latter was found among women in the current project (chapter 6), there was weak evidence that health behaviours are cross-sectionally associated with work stressors among women at WII phase 3 (table 9.1).

Table 9.2 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after adjustment for behavioural factors associated with diabetes during 15 years of follow-up among women (N=1543)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	20/230	1.95 (1.17; 3.27)	
+ alcohol consumption		1.93 (1.16; 3.23)	2%
+ physical activity		1.93 (1.15; 3.22)	2%
+ dietary energy density		1.94 (1.13; 3.33)	2%
+ unhealthy behaviour score		1.88 (1.13; 3.14)	7%

Table 9.2 shows the mediating effect of health behaviours in the iso-strain-incident T2DM association among women. The first estimates presented in table 9.2 are from the maximally adjusted model controlling for potential confounders (age, employment grade, life events and height) in the iso-strain-incident T2DM association (HR 1.95: 95% CI 1.17; 3.27). Adjusting individually for health behaviours in addition to potential confounders did not result in any further substantial reduction in the hazard ratios. The health behaviour score explained 7% of the effect of iso-strain on incident T2DM, proving that the individual small mediating effect of each health behaviour was additive.

9.4.2.2 Direct biological effect

The direct biological pathway hypothesizes that chronic exposure to psychosocial stressors causes a chronic activation of the sympathetic nervous system resulting in pathophysiological changes in the body leading to increased cardiometabolic risk.

Table 9.3 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after adjustment for individual biological factors associated with incident type 2 diabetes during 15 years of follow-up among women (N=1543)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	20/230	1.95 (1.17; 3.27)	
+ Body Mass Index		1.82 (1.09; 3.03)	14%
+ waist circumference		1.91 (1.14; 3.19)	4%
+ Waist-hip-ratio		1.94 (1.16; 3.25)	1%
+ waist-height ratio		1.86 (1.11; 3.11)	9%
+ triglycerides		2.06 (1.23; 3.46)	n/a
+ HDL-cholesterol		1.92 (1.16; 3.22)	3%
+ systolic blood pressure		1.89 (1.13; 3.16)	6%
+ fibrinogen		1.98 (1.19; 3.33)	n/a
+ C-reactive protein		1.85 (1.10; 3.08)	9%
+ Interleukin-6		1.96 (1.18; 3.29)	n/a
+ von Willebrand factor		1.97 (1.19; 3.30)	n/a
+ factorVII		1.96 (1.17; 3.28)	n/a
+ metabolic syndrome		1.95 (1.17; 3.25)	n/a

Table 9.3 shows how biological factors individually mediate the effect of iso-strain on incident T2DM among the whole sample of women. Adding biological risk factors individually in the maximally adjusted confounding model revealed that BMI had the largest mediating effect in the iso-strain-incident T2DM association. Differences in BMI between the women exposed and not exposed to iso-strain explained 14% of the association between iso-strain and incident T2DM. Waist circumference, WHR and WHtR had a smaller mediating effect (percentage reduction in risk 4%, 1% and 9% respectively). Apart from obesity measures, only systolic blood pressure, HDL-cholesterol and CRP had a mediating effect of 6%, 3% and 9% respectively.

In order to investigate the overall mediating role of biological factors in explaining the iso-strain-incident T2DM association, biological factors were individually added in a model containing potential confounders and BMI (table 9.4). The metabolic syndrome (waist circumference >102cm men >88cm women; blood pressure \geq 130/85;

triglycerides ≥ 1.69 ; HDL-cholesterol ≤ 1.03 for men ≤ 1.29 for women) was used as a summary variable for cardiometabolic factors

Table 9.4 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after subsequent adjustment for biological factors during 15 years of follow-up among women (N=1530)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	20/230	1.95 (1.17; 3.27)	
+ BMI		1.82 (1.09; 3.03)	14%
+ BMI + HDL		1.77 (1.05; 2.98)	19%
+ BMI + blood pressure		1.81 (1.08; 3.02)	15%
+ BMI + metabolic syndrome		1.82 (1.09; 3.05)	14%
+ BMI + CRP		1.77 (1.05; 2.99)	19%
+ BMI + HDL + CRP		1.73 (1.03; 2.92)	23%
+ BMI + HDL + all inflammatory markers		1.65 (0.92; 2.89)	32%

Table 9.4 shows additive models for the overall mediating effect of biological factors in the iso-strain-incident T2DM association. The variables that were added in the confounder-adjusted model in addition to BMI were systolic blood pressure, HDL, CRP and the metabolic syndrome. These 4 variables were chosen as they were the only ones (in addition to obesity measures) that had a mediating effect in the iso-strain-incident T2DM association. The biological factors adding to the mediating effect of BMI were CRP and HDL-cholesterol, increasing the percentage reduction in risk from 14% to 19%. This means that the small mediating effect of CRP (9%) is partly but not entirely due to the association of CRP with BMI. When both CRP and HDL were included simultaneously in a model containing potential confounders and BMI the percentage reduction in risk increased to 23%. When all inflammatory markers were added in the model the percentage reduction in risk increased to 32%. Further addition of triglycerides and systolic blood pressure did not increase the percentage reduction in risk and thus estimates are not presented in table 9.4.

9.4.2.3 Investigation of overlap between direct and indirect pathways

In order to investigate whether the small mediating effect observed through health behaviours was independent of biological risk factors, the unhealthy behaviour score was added in the maximally adjusted model containing all biological mediators. These results are presented in table 9.5.

Table 9.5 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after adjustment for biological behavioural factors after 15 years of follow-up among women (N=1523)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	20/230	1.95 (1.17; 3.27)	
+ unhealthy behaviour score		1.88 (1.13; 3.14)	7%
+ biological risk factors		1.65 (0.92; 2.89)	32%
+ biological risk factors + unhealthy behaviour score		1.68 (0.94; 3.02)	28%

Table 9.5 shows the combined mediating effect of behavioural and biological risk factors among the whole sample of women. The 7% reduction in risk observed when the unhealthy behaviour score was added in the confounder-adjusted model was not additive on the 32% risk reduction when biological factors (BMI, HDL and inflammatory markers). This indicates that any mediating effect of health behaviours was through biological factors. In other words, the small mediating effect of health behaviours (7%) is working through changes in obesity and/or HDL-cholesterol and/or inflammation.

9.4.3 Sensitivity analysis: Mediating pathways among low grade and obese women

Sensitivity analysis was performed in order to examine whether mediations differed among the sub-groups of obese and low grade women. The effect of iso-strain on incident

T2DM was found to be higher among these sub-groups compared to the whole sample (chapter 7, table 7.7).

9.4.3.1 Mediating pathways among obese women

Table 9.6 Cross-sectional associations between iso-strain and factors associated with incident type 2 diabetes at phase 3 of the WII study among OBESE women (N=226)

	No iso-strain (N=188)	Iso-strain (N=38)	<i>p-value for difference</i>
Alcohol consumption (%)			
no	37.9 (75)	25.6 (10)	
moderate	59.1 (117)	69.2 (27)	
heavy	3.0 (6)	5.1 (2)	0.31
Physical activity (mean)	2.82 (0.19)	2.49 (0.43)	0.49
Dietary energy density (mean)	1.01 (0.02)	0.98 (0.05)	0.54
Unhealthy behaviour score	0.77 (0.05)	0.71 (0.14)	0.66
Body Mass Index (mean)	33.6 (0.25)	35.0 (0.61)	0.022
Waist circumference (mean)	95.5 (0.72)	99.0 (1.71)	0.052
Waist-hip ratio (mean)	0.86 (0.005)	0.88 (0.013)	0.32
Waist-height ratio (mean)	0.59 (0.004)	0.61 (0.011)	0.052
Triglycerides (mean)	1.67 (0.07)	1.61 (0.10)	0.70
HDL-cholesterol (mean)	1.44 (0.03)	1.47 (0.05)	0.60
Systolic blood pressure (mean)	124.3 (0.97)	125.2 (2.04)	0.73
Fibrinogen (mean)	2.82 (0.05)	2.80 (0.09)	0.81
C-reactive protein (mean)	4.32 (0.33)	4.01 (0.69)	0.70
Interleukin-6 (mean)	3.19 (0.18)	2.59 (0.19)	0.16
von Willebrand factor (mean)	113.8 (3.05)	112.6 (6.79)	0.87
Factor VII (mean)	99.1 (1.78)	107.8 (6.45)	0.08
Metabolic syndrome (%)	38.6 (76)	43.6 (17)	0.56

Table 9.6 shows that compared to the main analysis in table 9.1, the association between all the obesity measures and factor VII was stronger and reached statistical significance among the sub-group of obese women. The higher BMI in those with iso-strain indicates that, among obese women, those who are also exposed to iso-strain are, on average, more obese than those not exposed.

Table 9.7 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after adjustment for behavioural factors associated with incident type 2 diabetes during 15 years of follow-up among OBESE women (N=225)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	10/37	3.00 (1.40; 6.46)	
+ alcohol consumption		3.26 (1.51; 7.05)	+11%
+ physical activity		3.00 (1.39; 6.49)	n/a
+ dietary energy density		3.88 (1.83; 9.91)	+30%
+ unhealthy behaviour score		3.08 (1.43; 6.23)	+4%

Table 9.7 shows that health behaviours have no mediating role in the iso-strain-incident T2DM association in the sub-group of obese women. Instead, there is an increase in the effect of iso-strain on incident T2DM after adjustment for these variables. This means that, among obese women, some of the health behaviours (alcohol consumption and diet) were more adverse in those *not* exposed to iso-strain, confounding thus the association between iso-strain and incident T2DM in a way to dilute the effect.

Table 9.8 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after subsequent adjustment for biological factors during 15 years of follow-up among OBESE women (N=225)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	10/37	3.00 (1.40; 6.46)	
+ waist-height ratio		2.65 (1.18; 5.72)	18%
+ waist-height ratio + HDL		2.42 (1.08; 5.39)	29%
+ waist-height ratio + blood pressure		2.64 (1.18; 6.50)	18%
+ waist-height ratio + metabolic syndrome		2.53 (1.09; 3.05)	23%
+ waist-height ratio + CRP		2.53 (1.19; 6.56)	23%
+ waist-height ratio + metabolic syndrome + CRP		2.42 (1.10; 5.40)	28%
+ waist-height ratio + HDL + CRP		2.40 (1.07; 5.35)	30%
+ waist-height ratio + HDL + all inflammatory markers		1.95 (0.92; 4.89)	53%

Table 9.8 shows effect mediations after adding biological factors in a model containing confounders and WHtR (table 9.12). WHtR was chosen instead of BMI as the variation of this measure would be higher than BMI among this sub-group of women with a $BMI \geq 30 \text{ kg/m}^2$. When HDL and all inflammatory markers were added together in a model containing WHtR, the percent reduction increased to 53%. This is higher than the 32% of effect explained by biological factors in the whole sample of women. These results among the sub-group of obese women should be interpreted with caution as they are based on a relatively small group of women (N=225) with only 37 of them being exposed to iso-strain and with only 10 T2DM cases among the exposed.

9.4.3.2 Mediating pathways among low-grade women

Table 9.9 Cross-sectional associations between iso-strain and factors associated with incident T2DM at phase 3 of the WII study among LOW GRADE women (N=528)

	No iso-strain (N=469)	Iso-strain (N=59)	<i>p</i> -value for difference
Alcohol consumption (%)			
no	40.6 (203)	42.9 (27)	
moderate	58.6 (293)	55.6 (35)	
heavy	0.8 (4)	1.6 (1)	0.76
Physical activity (mean)	3.01 (0.16)	2.53 (0.36)	0.49
Dietary energy density (mean)	0.99 (0.13)	0.97 (0.38)	0.49
Unhealthy behaviour score	0.80 (0.03)	0.92 (0.10)	0.23
Body Mass Index (mean)	26.1 (0.18)	28.1 (0.65)	<0.001
Waist circumference (mean)	79.1 (0.49)	83.8 (1.69)	0.002
Waist-hip-ratio (mean)	0.81 (0.003)	0.83 (0.009)	0.043
Waist-height ratio (mean)	0.49 (0.003)	0.52 (0.011)	0.002
Triglycerides (mean)	1.32 (0.04)	1.44 (0.10)	0.29
HDL-cholesterol (mean)	1.62 (0.02)	1.58 (0.05)	0.42
Systolic blood pressure (mean)	118.6 (0.66)	117.9 (0.61)	0.70
Fibrinogen (mean)	2.65 (0.03)	2.60 (0.06)	0.52
C-reactive protein (mean)	2.37 (0.16)	2.34 (0.35)	0.95
Interleukin-6 (mean)	2.31 (0.10)	1.99 (0.13)	0.27
von Willebrand factor (mean)	114.2 (1.98)	110.2 (4.63)	0.50
factorVII (mean)	95.6 (1.29)	96.7 (4.62)	0.79
Metabolic syndrome (%)	13.3 (66)	19.1 (12)	0.21

Table 9.9 shows that obesity measures were higher among low grade women with iso-strain compared to low grade women with no iso-strain. Prevalence of the metabolic syndrome was higher among iso-strain women in the low grade, but this did not reach statistical significances. The unhealthy diet score was higher among low grade women with iso-strain compared to low grade women with no iso-strain but this also did not reach statistical significance.

Table 9.10 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after adjustment for behavioural factors associated with diabetes during 15 years of follow-up among LOW GRADE women (N=526)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	8/56	4.26 (1.85; 9.78)	
+ alcohol consumption		4.23 (1.54; 9.72)	1%
+ physical activity		4.20 (1.83; 9.65)	2%
+ dietary energy density		3.91 (1.12; 8.99)	10%
+ unhealthy behaviour score		3.83 (1.53; 9.19)	14%

Table 9.10 shows that the mediating role of health behaviours in the iso-strain-incident T2DM association among low grade women is higher than in the whole sample of women (14% vs. 7%). Dietary energy density explained 10% of the iso-strain-incident T2DM association within this sub-group.

Table 9.11 Hazard Ratios (95% Confidence Intervals) for the effect of iso-strain on incident type 2 diabetes after subsequent adjustment for biological factors during 15 years of follow-up among LOW GRADE women (N=524)

Adjustments	exposed cases/ total exposed	HR (95% CI)	% risk reduction
age, employment grade, life events, height	8/56	4.26 (1.85; 9.78)	
+ BMI		3.49 (1.50; 8.13)	24%
+ BMI + HDL		3.36 (1.37; 7.88)	29%
+ BMI + metabolic syndrome		3.54 (1.62; 8.30)	23%
+ BMI + HDL + metabolic syndrome		3.42 (1.45; 8.00)	26%

Table 9.11 shows the mediating effect of additive models of biological factors among low grade women. Addition of HDL and the metabolic syndrome simultaneously in a model containing confounders and BMI resulted in a smaller reduction in percent risk compared to the model containing only confounders, BMI and HDL (26% vs. 29%). As with the obese sub-group, results from this sub-group of women should be interpreted with extra caution as they are based on only 524 women with just 8 exposed T2DM cases.

9.5 Comparison to other studies

From the very few epidemiological studies that investigated the association between psychosocial work stressors and T2DM (Kroenke et al, 2007; Norberg et al, 2007; Kumari et al, 2004; Agardh et al, 2003; Leynen et al, 2003), none has specifically aimed at systematically investigating the pathways involved. In addition, behavioural and biological factors were treated as potential confounders instead of mediators in those studies. The background theory supporting the link between psychosocial stressors and T2DM (McEwan, 1998; Brunner, 1997; Dallman et al, 2005) as well as small-scale experimental studies (Chida & Hamer, 2008), clearly indicate that exposure to psychosocial stressors could potentially affect health behaviours and biological risk factors. Adjusting for these factors as potential confounders and presenting relative risks after adjustment without discussion of mediation of effect is a case of over-adjustment.

In the Stockholm Diabetes Prevention Program (Agardh et al, 2003), from a series of potential ‘confounders’, including smoking, physical activity, BMI and WHR, the authors found only physical activity to substantially (defined by the authors as $\pm 15\%$ reduction in effect) decrease the effect of job strain on prevalent T2DM after adjustment. The authors thus adjusted their models only for physical activity but the effect before adjustment was not presented in the paper so it was not possible to calculate the exact proportion of the association explained by physical activity in that study. In the Vasterbotten Intervention Programme (Norberg et al, 2007) the effect of job strain on prevalent T2DM was adjusted for BMI, but again the findings before this adjustment were not presented in the paper. A study that took account of several ‘confounders’ and presented results before and after adjustment was the Nurses’ Health Study II (Kroenke et al, 2007) looking at the effect of

job strain on incident T2DM. That study however failed to show an association between job strain and incident T2DM, thus any adjustment for behavioural and biological factors was not informative.

In a WII publication, Chandola et al (2008) investigated behavioural and biological pathways between iso-strain and incident heart disease. Even though the outcome was different from the current analysis, T2DM shares similar risk factors with CVD. That analysis used a different follow-up and stratified results by age group instead of gender and unlike the current analysis, behavioural and biological risk factors were coded into binary variables. For these reasons direct comparison with the current results is not easy.

In the paper by Chandola et al (2008), 32% of the effect of iso-strain on heart disease among younger (<50 years) participants was explained by behavioural and biological factors (inflammatory markers were not included). This is equivalent to the mediating effect by biological risk factors among women in the current project. Analysis looking at mediations among only the younger participants, could not be performed in the current results as the effect of work stressors on T2DM, unlike the case with heart disease, was absent in younger participants (chapter 7 table 7.7).

In general, both the current analyses and the paper by Chandola et al (2008) agree that around a third of the association between iso-strain and heart disease, and iso-strain and T2DM, is explained by behavioural and biological risk factors. Another publication from the WII study which investigated the effect of phase 1 and 2 psychological factors (but not work stressors) on heart disease, did not find evidence for a mediating effect by inflammatory markers (phase 3 fibrinogen, CRP and IL-6) (Nabi et al, 2008).

9.6 Summary and link to next chapter

This chapter examined the hypothesis that the association between psychosocial work stressors and incident T2DM is mediated partly through health behaviours and partly

through direct biological pathways involving cardiometabolic and inflammatory risk factors. Based on the specific objectives, the current chapter identified that:

1. Health behaviours, namely alcohol consumption, physical activity and dietary energy density were not associated with iso-strain among women. Biological factors were also not linked to iso-strain among women, apart from obesity, as well as CRP and vWf, which were weakly associated with iso-strain.
2. The current results show evidence supporting that the direct biological pathway is the major linking work stressors to T2DM among women in the WII study. The indirect pathway through health behaviours explained only 7% of the effect of iso-strain on incident T2DM. BMI, individually, had the highest mediating effect (14%). Addition of HDL and the inflammatory markers with BMI explained 32% of the effect of iso-strain on incident T2DM among women.
3. The small indirect mediating effect of health behaviours in the iso-strain-incident T2DM association was not independent of biological factors.

This chapter investigated the main hypothesized pathways linking psychosocial work stressors to incident T2DM, which was the third aim of the project. The current results support evidence for a direct biological pathway but not an indirect behavioural pathway linking work stressors to T2DM. The following chapter (thesis discussion chapter) will discuss findings from all results chapters addressing the main project aims.

Chapter 10: Discussion

Type 2 diabetes is a multi-factorial disease of impaired glucose metabolism leading to several life-disabling complications and premature death, especially from heart disease. Determinants of T2DM span from social to behavioural to cardiometabolic to genetic. The psychological state has been linked to diabetes as early as the 17th century from observations that states of prolonged stress preceded the development of diabetes. Nowadays, psychosocial stressors, such as social isolation and stressful working conditions are hypothesized to have a pathophysiological impact. Such stressors have been implicated in the pathogenesis of CVD (Brotman et al, 2008). Despite the links between CVD and diabetes, only a limited amount of research concentrates on the involvement of psychosocial stressors in diabetes. Psychosocial work stressors have gained attention as important factors contributing to heart disease. The effect of such work stressors in diabetes development is under-researched, and their impact has been largely unknown. In addition, the main hypothetical pathways linking psychosocial stressors to cardiometabolic disease, in general, have not been supported by empirical findings. This project investigated the effect, impact and mechanisms between psychosocial work stressors and T2DM. This final chapter includes a summary of the results (presented in chapters 5-9) addressing the main aims of the thesis (chapter 3), followed by a detailed discussion of the main findings. Following this, the strengths and limitations of the project are addressed and finally implications for research and policy are discussed.

10.1 Summary of results

10.1.1 Incident T2DM and effect of psychosocial work stressors (chapters 5-7)

The crude T2DM incidence rate over the 21 year follow-up period (1985-2004) of around 2 cases per 1000 person-years at risk was similar to previous studies in the UK, other western European countries and the US, indicating that the study sample, even though strictly white-collar, is representative enough of the overall English middle-aged population. The incidence rate in the period 1991-2004 (phases 3-7), which was the

follow-up period used for the investigation of the effect of psychosocial work stressors on incident T2DM, was 4.8 cases per 1000 person-years. Overall, the incidence of T2DM among WII participants tended to increase, as in the general population (Gonzalez et al JECH 2009). The secular increase in obesity prevalence observed in the UK (documented in the Health Survey for England) is probably the main reason for the increasing incidence of T2DM observed in younger age groups in the WII study over time. The repeat OGTT screening design in WII identifies cases early in the course of disease and this is reflected in the decreasing T2DM incidence rate evident during follow-up in those aged 55 years and over. In other words, the 5-yearly screening protocol leads to a shift in the apparent onset of T2DM to younger ages.

The current results extend the evidence on socioeconomic, psychosocial, behavioural and biological factors associated with incidence of T2DM. Employment grade was strongly and inversely associated with incident T2DM in both men and women. The degree upset by life events was the only outside-work stressor associated with T2DM risk. Among the health behaviours, physical activity and diet were associated with incident T2DM in both men and women, while moderate alcohol consumption was associated with lower risk among women and current smoking with an increased risk among men. Among the biological risk factors, BMI was as predictive of T2DM risk as measures of central obesity among participants of the WII study. Blood pressure, triglycerides, HDL-cholesterol and inflammatory markers were associated with incident T2DM after controlling for BMI.

The association between psychosocial work stressors and incident T2DM differed by gender. High job demands in combination with low job control (job strain) were associated with a 65% higher risk of T2DM among women and this rose to 2-fold for women reporting simultaneous low work social support (iso-strain). This effect was robust to adjustment for SEP, outside work stressors and height. No association between job strain and iso-strain was observed among men. The effect of high ERI was in the same direction, again opposite in men and women, with a protective effect among men (which did not reach statistical significance) and a harmful effect of 2-fold higher T2DM

risk among women. This effect of high ERI among women was not attenuated by adjustment for SEP, outside work stressors and height. The effect of job strain and iso-strain was higher among low grade participants (including men) and participants who were obese at baseline (only women).

10.1.2 Impact of psychosocial work stressors on incident T2DM (chapter 8)

The proportion of T2DM cases attributed to job strain and iso-strain among exposed women in the Whitehall II study was 35% and 44% of total cases respectively, assuming a causal association. The estimated impact (population attributable risk) of job strain in the whole Caucasian Whitehall II female population, free from T2DM at phase 3, was 15% of total T2DM cases. The respective impact for iso-strain was 10% of total cases. These estimates of impact are similar to those reported in the literature for work stressors in relation to other health outcomes and are similar to estimates of impact for unhealthy behaviours. After elimination of obesity or the metabolic syndrome, additional elimination of work stressors would have a relatively small impact on diabetes burden.

10.1.3 Pathways between psychosocial work stressors and incident T2DM (chapter 9)

The findings of the last results chapter support evidence that the direct cardiometabolic/inflammatory pathway proposed in the literature is an important pathway linking psychosocial work stressors to T2DM. Obesity, cardiometabolic risk factors and markers of inflammation explained 1/3 of the effect of iso-strain on incident T2DM. This proportion of effect was largely explained by obesity, HDL-cholesterol and systemic inflammation. The results do not support the proposed indirect behavioural pathway as important in the link between psychosocial work stressors and T2DM. There was only a small mediating indirect effect through health behaviours, which was working through changes in obesity and other biological risk factors. Plausible alternative pathways for the effect of psychosocial work stressors on incident T2DM are discussed in this chapter.

The following sub-sections further discuss the results addressing the main aims of the current project: (i) Effect of psychosocial work stressors on risk of T2DM; (ii) Impact of psychosocial work stressors on incident T2DM; and (iii) Pathways between psychosocial work stressors and T2DM.

10.2 Effect of psychosocial work stressors on incident type 2 diabetes

10.2.1 Is the observed association between psychosocial work stressors and T2DM causal?

Chapter 7 included a detailed investigation of the validity of the association between psychosocial work stressors and incident T2DM. A valid association between an exposure and an outcome does not prove causality however. The current sub-section will further discuss the validity (chance, bias and confounding) of the association between psychosocial work stressors and T2DM, followed by a discussion of criteria for judging about causality.

10.2.1.1 Validity of the association

10.2.1.1.1 Chance (random error)

In a given sample, there is a chance that an estimated effect of an exposure on an outcome either over-estimates (potentially leading to type I error) or under-estimates (potentially leading to type II error) the true effect (i.e. effect in the population from which the sample was drawn) due to random variation in the selected sample. The smaller the sample size the higher is the probability of a chance finding.

In the case of the current analysis the observed effect of work stressors was among a sample of 1729 women, of whom 230 were exposed to iso-strain and 250 to effort-reward imbalance at analysis baseline. During follow-up, 21 of these exposed women developed T2DM. Despite the relatively low number of exposed cases, the 95% confidence intervals for the main effect of iso-strain (HR 1.95: 95% CI 1.17; 3.27) and ERI (HR 1.84: 95% CI

1.01; 3.37) indicate that it can be stated with 95% certainty that the observed effect is not a chance finding.

Given the above, it is not likely that chance explains the association between work stressors and T2DM risk in women. However, a larger sample size would provide higher power and higher precision, strengthening even further the validity of the association in terms of random error.

10.2.1.1.2 Bias (systematic error)

Bias, also called systematic error, refers to errors introduced to the results due to flaws/inaccuracies in the processes of sample selection, data collection or loss to follow-up (in the case of cohort studies). There are two types of bias: (i) information bias; and (ii) selection bias.

10.2.1.1.2.1 Information bias

Information bias is based on the notion that if the exposure or outcome of interest (or another key variable) are not accurately measured, then the observed effect of an exposure on an outcome would be unrealistic of the effect in the population from which the study sample was drawn. If information bias is selective (depends on the outcome of interest) then the effect estimate may be increased, decreased or even reversed.

Information bias could have affected the observed effect of higher T2DM risk among women exposed to psychosocial work stressors, if exposure to psychosocial work stressors was over-reported by women who had an elevated risk of developing T2DM during follow-up. As discussed extensively in the thesis, obesity is the most important risk factor for T2DM in the current sample. As there is no gold standard for validating self-reported psychosocial work characteristics, it is impossible to assess the extent of under- or over-reporting of psychosocial work stressors. One way of addressing this issue is to determine whether the proportion of participants exposed to psychosocial work stressors is higher in the obese compared to the non-obese. This was addressed in chapter

7 and it was found that indeed prevalence of psychosocial work stressors was higher among obese participants at baseline. The analysis was thus repeated, excluding participants with a $BMI \geq 35 \text{ kg/m}^2$ (class II and III obesity) (chapter 7, table 7.12). Only these participants were excluded as it was speculated that they would be more likely to over-report adverse psychosocial characteristics due the morbid nature of their obesity and related disability.

Excluding these participants from analysis resulted in an attenuation of the effect of iso-strain among women from a hazard ratio of 1.95 to 1.58. This could have three meanings: (i) women with extreme obesity over-report adverse psychosocial work experiences hence the observed association between iso-strain and incident T2DM (i.e. a biased effect estimate); (ii) exposure to iso-strain contributed to the higher obesity among very obese participants and hence elevated the risk of T2DM (i.e. extreme obesity as a mediator in the work stressors-incident T2DM association); and (iii) the effect of iso-strain is higher among the obese thus exclusion of these participants dilutes the overall effect (i.e. interaction between work stressors and obesity).

In the first of the 3 explanations, over-reporting of psychosocial work stressors by obese participants could introduce systematic error in the results and an over-estimation of the effect of work stressors on incident T2DM. Exposure to iso-strain was not associated cross-sectionally with BMI however (chapter 9, table 9.1), therefore it is unlikely that obese participants over-reported their exposure to psychosocial work stressors. On the other hand, there was evidence presented in chapters 7 and 9, that obesity is both an effect modifier (chapter 7, table 7.9) and a mediator (chapter 9, table 9.3) in the work stressors-T2DM association, supporting thus the latter two explanations. In addition, the effect of ERI on incident T2DM was not attenuated by the exclusion of morbidly obese participants. Given this, it could be stated that extremely obese participants are most likely a group of participants in whom the effect of work stressors on incident T2DM is higher than the rest of the sample rather than a group of participants who over-report adverse working conditions.

10.2.1.1.2.2 Selection bias

The role of selection bias in the results was addressed in chapter 4 (sub-section 4.4.1.7) and chapter 7 (sub-section 7.8.2). Selective drop-out can result when participants who are lost to follow-up differ in key characteristics compared to those who remain in the study. This selective drop-out has the potential to distort the observed effect of an exposure on an outcome. As commonly encountered in longitudinal studies, there was loss to follow-up between recruitment (phase 1) and the analysis baseline (phase 3) with 17% not participating in the present study. Key characteristics of the participants lost to follow-up compared to those who participated at phase 3 are presented in chapter 4, table 4.7.

In addition, selective drop-out during follow-up from phase 3 to phase 7 may introduce further bias in the results. Key characteristics of the participants lost to follow-up from phase 3 to phase 7 compared to those who participated at phase 7 were also given in chapter 4, table 4.8. Participants lost to follow-up from phase 1 to phase 3 and from phase 3 up to phase 7 were more likely to be women, were younger, were more likely to come from the low employment grades, more likely to be exposed to psychosocial work stressors and had a higher mean BMI.

The fact that participants exposed to psychosocial work stressors were more likely to drop out during follow-up than those not exposed, could potentially lead to type II error and a dilution of a possible effect of work stressors on T2DM. This could partly explain the lack of effect of work stressors on incident T2DM among men. However, table 7.10 in chapter 7 shows that this selective drop out was also present among women, in whom an effect of work stressors was apparent. Therefore it is not likely that selection bias due to selective drop out is the reason for the lack of effect among men, as there is no plausible explanation as to why such information bias did not dilute the effect among women.

10.2.1.1.3 Confounding

Confounding can alter the results of a study by causing an unrealistic estimate of the effect in the population from which the study sample was drawn. In chapter 7, table 7.5

shows the effect of psychosocial work stressors after adjusting for the main confounders, namely age, employment grade, life events and height. Age could confound the association between work stressors and T2DM, as the risk of T2DM increases with age (chapter 6, table 6.2) and reporting of exposure to work stressors also differs by age (chapter 7, tables 7.2 and 7.3). Employment grade could also confound the association as employment grade has a strong inverse relation with incident T2DM (table 6.2) and reporting of work stressors is more common among lower grade participants (tables 7.2-7.3). The same applies for those exposed to adverse life events outside the workplace. Height could be considered as a non-specific marker of rate of childhood growth and development (Webb et al, 2008)

Therefore the observed effect of work stressors on incident T2DM could be partly explained by the older age and/or lower SEP and/or more adverse life events either recent or in early life among those exposed to work stressors. Several other potential confounders, including social, psychosocial and psychological factors (see chapter 4) were considered, but these were not included in the models as these were either not associated with the exposure of interest (work stressors) or the outcome of interest (T2DM) (chapter 6). The effect of work stressors was also assessed after additional adjustment for participants' psychological state during the 2 weeks prior to questionnaire completion, as well as the effect of departmental relocation, after speculation that these variables might have affected participants' reporting of adverse work characteristics.

After adjustment for all of the above factors, women exposed to iso-strain at baseline had a 2-fold higher risk for developing T2DM compared to women not exposed to iso-strain. Given that the main confounding variables (age and employment grade) were accurately measured in the WII study, it is unlikely that residual confounding is operating after adjustment. Additional adjustment for BMI, HDL-cholesterol and inflammatory markers in chapter 9 (table 9.4) attenuated this effect. As already mentioned, these biological factors are considered as potential mediators (i.e. in the causal pathway) between psychosocial work stressors and incident T2DM and not as potential confounders.

Given the above, it can be stated with relative certainty that the effect of psychosocial work stressors on incident T2DM among women is not confounded by age, SEP, adverse life events outside the workplace, height, or by the psychological state of participants during questionnaire completion. Residual confounding may however be operating as even though all possible covariates which could have affected the association were accounted for (chapter 6), other covariates, which were not assessed in the WII study, may confound the results. Such factors could be early life social or biological adversity (Langenberg et al, 2006; Langenberg et al, 2007), for which little information is available in the WII study. Even though adult height was accounted for, this cannot be considered as a specific marker of childhood adversity. Father's social class, which may be considered a marker of SEP in childhood, was not associated with incident T2DM in this analysis (chapter 6). Other early life adversity marker variables such as birth weight and leg length were not associated with psychosocial work stressors (results not shown).

Overall, even though residual confounding may be operating in the results, it is unlikely that this is at the extent to explain the ~2-fold higher risk of T2DM among work stressed women.

10.2.1.2 Criteria for judging about causality

The Bradford Hill criteria, a set of criteria proposed by the epidemiologist Sir Austin Bradford Hill in 1965, can help evaluate whether an observed valid association between an exposure and an outcome is likely to be causal (Bradford Hill, 1965). These criteria were proposed for judging causality in associations from epidemiological studies (particularly observational), which were impossible (or very difficult) to assess experimentally. The association between work stressors and T2DM falls in this category of associations. An intervention which induces chronic psychosocial work stress on people would be unethical. However, observing short-term psychoneuroendocrine effects of acute psychosocial stress is not unethical and indeed such evidence is abundant in the literature and supports the biological plausibility of observations from epidemiological studies. Biological plausibility, together with other criteria for judging about causality in

the work stressors-incident T2DM association are discussed below. It should be mentioned here that the Bradford Hill criteria, even though extremely useful, are not sufficient for demonstrating causality.

10.2.1.2.1 Coherence and biological plausibility

Evidence from smaller-scale studies (including studies of induced experimental psychosocial stress), as well as animal studies supporting the coherence and biological plausibility of the association between psychosocial work stressors and T2DM were given in chapter 2.

In summary, these studies consistently show that acute experimental psychosocial stress can activate the acute stress response, as indicated by increased levels of stress hormones, such as catecholamines and cortisol. In addition (and more relevant to the current project), individuals reporting exposure to chronic psychosocial stressors, including work stressors, have been found to have higher baseline levels of cortisol (indication of chronic activation of the HPA axis), as well as lower heart rate variability and delayed blood pressure recovery following stress (indication of chronic activation of the adrenal-medullary axis). Despite this association between psychosocial stressors and biomarkers of neuroendocrine activation, there is inconsistent evidence linking psychosocial work stressors to biomarkers of cardiometabolic risk, such as increased visceral fat, blood lipids, blood pressure and markers of inflammation.

Despite the lack of strong evidence linking psychosocial work stressors to cardiometabolic risk biomarkers, the association between these stressors and cortisol could provide a biologically plausible link with T2DM. As described in the introduction chapter, cortisol interferes with the proper functioning of insulin by antagonising its actions, contributing thus to hyperglycaemia. This potential mechanism through cortisol together with other are discussed in a following sub-section of the current chapter.

10.2.1.2.2 Strength, temporality, and dose-response relationship

Strong associations are less likely to be explained by residual confounding or bias. If the exposure assessment *precedes chronologically* the outcome assessment, then the case for a causal association is strengthened. The association between psychosocial work stressors and incident T2DM observed in the current project was relatively strong compared to the effects of other factors (see chapter 6). For example the hazard ratio of ~2 observed in the case of iso-strain, is higher than the effect of an unhealthy diet (HR=1.7) and similar to the effect of smoking (HR=2.1).

‘Reverse causality’ meaning that in an association between two variables, the outcome causes the exposure instead of vice versa, may be a problem mostly in cross-sectional and case-control studies. The association between work stressors and T2DM was prospective in nature, as work stressors were assessed between 1991-93, while T2DM was ascertained from 1993 up to 2004. This temporal association strengthens the case for causality. Exclusion of prevalent T2DM cases at baseline (1991-1993) eliminates any uncertainty about reverse causality (i.e. diabetics being more prone to report more adverse working conditions and hence higher work stress).

Dose-response association refers to the phenomenon where an increase in the exposure causes an increase in the magnitude of effect. Despite the inability to generate evidence for a dose-response relationship in the current results (the variables of job strain, iso-strain and ERI were not ordered categorical), the observation that the individual components of the demand/control/support model (high job demands, low job control and low work social support) were not associated with incident T2DM but their combinations (i.e. job strain and iso-strain) were, can provide evidence towards causality. In more detail, combination of high demands and low control (job strain) increased T2DM risk by ~65% and addition of low work social support to job strain (iso-strain) increased this effect to 2-fold. This accumulative increase in risk associated with subsequent addition of psychosocial work stressors may be regarded as a form of dose-response relationship. .

10.2.1.2.3 Consistency and analogy

Consistency refers to the situation where, the effect of an exposure on an outcome is observed in different studies with different study designs and populations. Analogy refers to existence of similar observed associations to the association under investigation.

During the past 15 years a body of evidence was generated supporting an involvement of psychosocial stressors in the pathology of cardiometabolic disease, especially heart disease. Several types of psychosocial stressor were investigated, the major ones being lack of social support and adverse psychosocial work characteristics. A review of prospective cohort studies on the role of psychosocial stressors in the aetiology and prognosis of heart disease reported that the proportion of aetiologic studies reporting a strong or moderate association was 20 out of 30 for social support and 12 out of 17 for psychosocial work characteristics (Kuper et al, 2002). The authors concluded that, based on prospective epidemiological data, there was evidence for an association between psychosocial work characteristics and heart disease aetiology. A more recent meta-analysis also confirmed these findings (Kivimaki et al, 2006).

The only review investigating the involvement of psychosocial stressors in T2DM (Chida et al, 2008) concluded that there is inconclusive evidence for an association due to the limited number of studies and conflicting results. However, the current results are consistent with the few studies that investigated the role of work stressors on risk of T2DM (see systematic review, chapter 2). This consistency can be regarded as strengthening the case for causality.

Analogous findings from the WII study linking psychosocial work stressors to obesity (Brunner et al, 2007) and the metabolic syndrome (Chandola et al, 2006), further strengthen the case for a causal association between psychosocial work stressors and T2DM risk.

10.2.1.2.4 Reversibility (intervention studies)

As described in the beginning of this sub-section, the strongest evidence for a causal association between an exposure and an outcome comes from intervention studies, but these are impossible to conduct in the case of work stressors. However, what could be done, is observing the effect of removal (or reduction) of exposure to psychosocial work stressors on neuroendocrine responses and health outcomes. Such evidence strengthens further the case for a causal association and is discussed below.

In a stress prevention trial among bus drivers, 54 male inner-city bus drivers reporting high effort-reward imbalance, participated in a 12-week stress management program (Aust et al, 1997). The intervention included relaxation; coping with anger and excessive work commitment (high need for control); management of conflicts with superiors; and recommendations for structural changes at work. After 12 weeks, the mean level of 'need for control' was significantly reduced in the intervention group compared to the control group. This theory-based worksite stress management program showed beneficial psychological effects among participants exposed to work stressors.

In an intervention study in Sweden, supervisors were randomly assigned on training for provision of appropriate esteem and recognition to employees (intervention group). A group of supervisors in whom no training was carried out served as the control group. Compared to employees who worked under the non-trained supervisors, those who worked under the newly trained supervisors had reduced cortisol levels during the working day (Theorell et al, 2001), proving that removal or reduction of work stressors does influence neuroendocrine activation among employees.

In a study involving reduction of objective workload levels among UK driving examiners, the intervention group reduced their working hours from 9 driving tests per day at 45-minute intervals to 8 tests per day at 50-minute intervals, or 7 tests per day at 60-minute intervals. Compared to the control group (no alterations in working conditions), in the intervention group, reduced workload resulted in an increase in job satisfaction, reductions in anxiety and lowered heart rate (Parkes et al, 1986; Parkes, 1995). Similarly, in the Netherlands, 30 male driving examiners were randomised into 3

groups differing in working conditions over three weeks. The 3 groups performed 11, 10 and 9 driving tests per day respectively. During the 3 week period, mental efficiency was drastically reduced in the 11-test condition. Adrenalin levels were higher in the afternoon among the 11-tests group and remained so until the end of the day suggesting that, when working the intense (11-test) schedule, examiners cannot relax easily. Repeatedly elevated adrenaline levels, as previously mentioned, is marker of activation of the acute stress response. In addition, instructors working in the 11-test schedule had poorer sleep quality during the 3-week period. Finally, a carry-over effect of tension in the evening to the following morning was noted only in the 11-test group (Meijman et al, 1992).

In a study investigating the effects of work-related stress reduction on depressive symptoms among Japanese blue-collar workers, stressor reduction measures were initiated in two intervention worksites, which were compared to three, matched, control worksites. Worksite stressor reductions included the enhancement of machine speed and performance, a reduction in the number of checks required on the production machines, increased 'on-the-job' training, standardization of the production process, and an increase in supervisor support brought about by the introduction of sub-leaders. Depressive symptoms decreased in the intervention compared to the control worksites and this effect was still evident at the 2-year follow-up assessment. In addition, the proportion of participants who had 1-5 days of sick leave in the past year decreased in the intervention groups but not in the control groups (Kawakami et al, 1997).

There is therefore good evidence, though still limited to a few studies, that interventions for a reduction of exposure to psychosocial work stressors do indeed benefit both the psychological and physical health of employees. This strengthens further the case for causality.

Overall, the association between psychosocial work stressors and T2DM observed in the current project was strong, prospective and followed a dose-response fashion. This association is both coherent and biologically plausible and is relatively consistent in the few studies that investigated it. Analogous effects have been also consistently shown for

heart disease. Finally, few intervention studies support that reversibility/reduction of symptoms occurs with removal/reduction of work stressors. Given these, it can be concluded that there is a strong case that the association between psychosocial work stressors and incident T2DM is causal. Probably the biggest obstacle for this statement is the lack of effect among men observed in the current analysis as well as other studies. This gender difference in effect is discussed in detail below.

10.2.2 Gender differences in the psychosocial effect

In chapter 7, a detailed investigation of the reasons for the observed gender differences in effect was carried out. Briefly, these gender differences could be explained, either due to a type I error in the effect among women, or a type II error in the effect among men. For type I error, confounding was excluded as all potential confounders (employment grade, life events, height, psychological state at the time of questionnaire completion, extra tensions due to anticipation of departmental relocation) were accounted for and the effect among women remained robust. The lack of effect among men is unlikely to be explained by type II errors as there was no evidence for gender differences in ascertainment of work stressors or diabetes, which could have diluted any effect of stressors in men but not in women. Potential social and biological explanations for gender differences are discussed below.

10.2.2.1 Potential social explanations for the gender difference in the effect psychosocial work stressors on incident T2DM

The following two potential social explanations for the gender difference in the effect of psychosocial work stressors on incident T2DM were investigated in chapter 7: (i) The effect of work stressors is higher among the low grade participants and hence the higher effect among women, who are concentrated in the low grades; and (ii) Men are more likely to ‘escape’ from exposure to psychosocial work stressors over time and thus are less affected. These two explanations will be discussed here.

10.2.2.1.1 The role of the interaction between psychosocial work stressors and employment grade

The results in table 7.13 in chapter 7 show that the gender interaction in effect is present within the high grade group but not within the low grade group (p for interaction=0.027 vs. 0.35). Low grade men are the only sub-group of men in whom there is some evidence for an effect of psychosocial work stressors on incident T2DM. Due to the small number of participants in this group however ($N=168$) the precision of the effect is very low as indicated by the wide confidence intervals of the effect (HR 1.53: 0.42; 5.51). The effect of psychosocial work stressors on incident T2DM among the low grade men provides a suggestion that the gender differences in effect could be partly explained by a work stressor/employment grade interaction. In other words the grade of employment modifies the effect of work stress on incident T2DM, with the effect of work stressors being higher within the low grade compared to the middle/high grade. The very different proportion of participants in each employment grade among men and women may contribute to the observed gender difference in the effect of work stressors on incident T2DM. In the current analysis 35% of women are in the low grade compared to only 5% in men. However, this could not fully explain the gender differences as the effect of work stressors on incident T2DM among women is much higher within both the high (1.52 in women vs. 1.02 in men) and low (3.32 in women vs. 1.53 in men) grades.

10.2.2.1.2 The role of gender differences in repeated exposure to psychosocial work stressors

A second potential social explanation for the gender differences in the effect of psychosocial work stressors on incident T2DM could be that in the Whitehall II study, men exposed to work stressors are more likely to find ways to ‘escape’ compared to stressed women. This is supported by two lines of evidence. First, tables 7.2 and 7.3 (chapter 7) show that, cross-sectionally, as age increases the proportion of men exposed to psychosocial work stressors decreases, while the opposite holds for women. There is a trend of increasing prevalence of psychosocial work stressor exposure with increasing age amongst women (despite a small decrease in the oldest age group).

Secondly, psychosocial work stressors were assessed at phases 1 and 2 in the WII study. This provided an opportunity to investigate whether any differences in *repeated* exposure to these stressors exist between men and women. Such differences could provide a potential explanation for the gender differences observed as work stressed men may be more likely to find ways to ‘escape’ from work stressors compared to women. In order to further investigate that exposure to work stressors decreases with time in men more than in women, the repeated exposure to work stressors (job strain) from phases 1-3 was determined in men and women separately. The results from this analysis confirm that the proportion of stressed women at phase 1 who remained stressed until phase 3 was higher compared to that in men (27.2% vs. 24.9%), although this gender difference in prevalence did not reach statistical significance. This indicates again that men are more likely to ‘escape’ from exposure to psychosocial work stressors than women.

Given that the risk of T2DM increases with increasing age over time (chapter 5), there are more T2DM cases among older participants, it could be argued that at the time that the rate of T2DM starts to increase, a substantial proportion of men who were exposed to psychosocial work stressors at phase 3 (analysis baseline) have managed to ‘escape’ from this exposure by phase 7. The same is unlikely to hold for women, for whom there is no evidence that exposure to psychosocial work stressors decreases with age or over time.

A potential explanation for this more successful ‘escaping’ capabilities among men may be that, in the civil service, men tend to go up the employment grade hierarchy at a greater extent than women (*Roberts et al, 1993*), probably resulting in an accompanying decrease in exposure to psychosocial work stressors, which are more prevalent in the lower grades. In contrast, the lower upward mobility in employment grade among women has the potential to cause repeated and sustained exposure to psychosocial work stressors over time.

In addition, departmental privatization which occurred between WII phases 2 and 3 and which was shown to increase perceived stress and morbidity among relocated employees

(Ferrie et al, 2001) may have increased exposure to work stressors at a greater extent among women rather than men. At phase 3, the proportion of stressed women who remained in the study could have increased, partly as a result of them having to take on managerial roles after reorganization of the workplace, which they did not wish to do so (Jane Ferrie personal communication).

10.2.2.2 Potential biological explanations for the gender difference in the effect of psychosocial work stressors on incident T2DM

Even though it was suggested in the previous sub-section that the gender differences in the effect of work stressors on T2DM risk could be partly explained by the higher proportion of women in the low employment grade and by gender differences in prolonged exposure to psychosocial work stressors over time, it would be good to also discuss some potential biological explanations as alternative. The term biological explanations refers in this case to gender differences in psychoneuroendocrine activation resulting from exposure to psychosocial work stressors.

Evidence supporting such differences comes from the Whitehall II psychobiology sub-study in which it was shown that even though men and women had similar salivary cortisol levels during the weekends, during working days women had significantly higher cortisol levels compared to men (Kunz-Ebrecht et al, 2003). As the only difference between work and non-work days is the exposure to the work environment, this may indicate that women are more sensitive to exposure to psychosocial work stressors, in terms of psychoneuroendocrine activation, compared to men. As described in the introduction chapter, cortisol levels are elevated by exposure to psychosocial stressors and can interfere in the normal regulation of blood glucose by altering the body's release and sensitivity to insulin, increasing thus the risk of T2DM (Brunner, 1997; McEwan, 1998,2000).

In addition, evidence for a potential gender difference in psychoneuroendocrine responses comes from an intervention study investigating stress-induced glucocorticoid sensitivity

(i.e. cortisol) in relation to testosterone levels (Rohleder et al, 2002). The experimental groups (differing only in testosterone levels) had the same level of stress-induced glucocorticoid levels, but those with high testosterone levels showed a steep increase in glucocorticoid sensitivity following the stress intervention. The authors conclude that the increase in glucocorticoid sensitivity after stress serves to protect the individual from detrimental increases of pro-inflammatory cytokines and this sensitivity is aided by testosterone. This may therefore provide a biological advantage for men over women in terms of the detrimental effects of chronic stress-induced elevated glucocorticoid levels.

Evidence for sex differences in the development of T2DM, especially in relation to activation of the innate immunity, has been shown consistently in the German MONICA/KORA study (Herder et al, 2008; Kolz et al, 2008). In that study, activation of innate immunity was related to T2DM in women but not in men. Activation of innate immunity is among the pathways linking psychosocial work stressors to T2DM, thus the gender differences observed in the MONICA/KORA study add to the evidence for a potential biological explanation for the gender differences in the effect of psychosocial work stressors on incident T2DM in the current project.

A drawback of the above biological explanations is that CVD shares common causal pathways with T2DM (hypertension, adverse lipid profile, inflammation, the metabolic syndrome, insulin resistance) and no evidence for a lack of effect of psychosocial work stressors on CVD risk among men was previously shown in the WII study (Bosma et al, 1998; Kuper et al, 2002) or other studies (Belkic et al, 2004). Also, work stress was associated with the metabolic syndrome in women as well as in men (Chandola et al, 2006). It would be expected that if psychosocial work stressors increase the risk of CVD among men, they should also increase the risk of T2DM. However, even though T2DM and CVD share common risk factors, they are different diseases, thus some of these risk factors may be more important for T2DM than for CVD. For example, insulin resistance is more important in the pathogenesis of T2DM than in CVD, as insulin is the hormone responsible for regulating blood glucose levels. The association between psychosocial stressors and CVD, in addition to elevated cortisol, also involves pathways through

decreased heart rate variability, arrhythmias, as well as sudden rupture of atherosclerotic plaques causing acute IHD (Brotman et al, 2007). Therefore, pathogenesis of T2DM may be more closely related to the neuroendocrine effects of chronic HPA axis activation (i.e. raised cortisol levels) than is CVD and hence gender differences in effect of psychosocial work stressors maybe observed in T2DM and not in CVD.

10.2.2.3 Discussion of gender difference in light of evidence from other studies

The previous studies that have investigated the association between psychosocial work stressors and T2DM were presented and discussed in a systematic review of the literature in chapter 2. From the 3 studies that have investigated the effect of psychosocial work stressors on T2DM in both genders, only one found evidence for an effect among men (Kumari et al, 2004). The other two studies (Agardh et al, 2004; Norberg et al, 2007) found evidence for an effect among women but not among men, as in the current project. A problem arises however in that the only analysis that found an effect among men (and in fact no effect among women) was from the Whitehall II study (Kumari et al, 2004), as is the current project. The potential explanations for this difference in results will be discussed below.

In the paper by Kumari et al (2004) looking at the effect of components of the demand/control/support model and the ERI model on incident T2DM, a different follow-up was used (WII phase 1 to 5) than the current project (WII phase 3 to 7). The importance of this is that at phase 1, diabetes was ascertained by self-reports only. In contrast, at phase 3, diabetes was ascertained by an OGTT in those participants who reported not having diabetes. Using phase 1 as the baseline could result in information bias due to inclusion of prevalent diabetes cases among the participants to be followed-up for ascertainment of incident T2DM. This could result in over-estimation of the effect of psychosocial work stressors on incident T2DM, as reverse causality would not be excluded. For example participants with prevalent diabetes may be more likely to report being exposed to psychosocial work stressors. This may be an explanation for the

presence of an effect for ERI on incident T2DM among men in the analysis by Kumari et al (2004) in contrast to the current results.

Another important difference between the current results and those by Kumari et al (2004) is that the current analysis restricted the study sample to only Caucasian participants while Kumari et al (2004) included ethnic minorities and adjusted for minority ethnic group. Such an adjustment does not completely remove the confounding introduced by inclusion of ethnic minorities. Inclusion of ethnic minorities may have therefore also contributed to an over-estimation of the effect of ERI on incident T2DM among men by Kumari et al (2004).

To summarise, it appears that there is a social element explaining the gender differences in the effect of psychosocial work stressors on incident T2DM. This social element involves an overall social disadvantage of women in the WII study, being concentrated in the low employment grades, where the effect of work stressors is higher and also being less able to 'escape' from work stressors over time, probably due to limited social mobility compared to men. In addition, evidence also suggests that there may be gender differences in psychoneuroendocrine activation after exposure to psychosocial stressors, with women being more vulnerable both in terms of cortisol responses to stress and the effect of related inflammation on T2DM. The current project did not specifically aim to investigate gender differences so these speculated explanations will not be further discussed.

10.2.3 Effect modifications in the association between psychosocial work stressors and T2DM

10.2.3.1 Effect modification by employment grade

Several studies provide evidence suggesting that any insults, whether these are biological, behavioural or psychosocial, have more effect in socially disadvantaged participants than the socially advantaged (Blane, 2006). This is referred to as the social vulnerability hypothesis (Blane, 2006). In the current project therefore, it was hypothesized that the

effect of psychosocial work stressors is higher among participants in the lower employment grades. Employment grade in the WII study is an accurate measure of income, education, working conditions and hence SEP (Marmot et al, 1991). This hypothesis was addressed in chapter 7 (tables 7.6-7.8). The findings indeed confirmed the hypothesis that psychosocial work stressors have a higher effect among the low grade participants (HR 2.61 for iso-strain) than among the middle/high grade participants (HR 1.15 for iso-strain) (p for interaction=0.040). When this effect modification was assessed for men and women separately, the same trend was observed but this was more apparent among women.

A potential explanation for this higher effect of psychosocial work stressors among the low grade participants could be that people with a lower SEP would probably have less resources, both material (housing conditions, money, etc.) and psychological (coping skills, sense of coherence etc.) to deal with extra stressors in the work environment. Material deprivation is important as it would be more difficult for people to deal with work stressors if they simultaneously experience poor housing conditions, financial insecurity and domestic conflicts. This does not mean that higher SEP people are 'immune' to such material deprivation; however evidence shows that material deprivation is associated with lower SEP (Bartley, 2004).

Similarly, deprivation of psychological resources is also more common among people of lower SEP. It has been shown that high sense of coherence, self-efficacy, self-esteem, and more favourable coping skills are more prevalent in higher rather than lower SEPs (Lundberg, 1974). All these factors could potentially buffer some of the effects of psychosocial work stressors on incident T2DM, leaving thus lower SEP participants more vulnerable to exposures to adverse working conditions. Even though data on material and mental deprivation were available in the WII study, investigation of such buffering effects was beyond the scope of the current project. Apart from buffering effects, some researchers suggest that being of low SEP could *per se* cause feelings of inferiority and subordination, thus leading to a type of social vulnerability to other psychosocial insults (Wilkinson, 2006).

10.2.3.2 Effect modification by obesity

As in the case of social vulnerability, some people may experience biological vulnerability. Biological vulnerability may refer to any condition which renders a person more vulnerable in terms of resilience of his/her body to pathophysiological insults. For example the effect of an insult, such as a psychosocial stressor, on a person already suffering from hypertension, an adverse lipid profile and insulin resistance, would probably be different than the effect on a healthy, fit person with a healthy cardiometabolic profile. Effect modification by body weight status may reflect both biological as well as social vulnerability, as obese people may face discrimination due to their excess body weight.

Based on this, it was hypothesized that the effect of psychosocial work stressors on incident T2DM would be higher among participants who were obese ($BMI \geq 30 \text{ kg/m}^2$) at the beginning of follow-up. As hypothesized, results from chapter 7 (tables 7.6-7.8) showed that indeed the effect of psychosocial work stressors on incident T2DM was higher among obese participants (HR 1.54 for iso-strain) than lean participants (HR 1.10 for iso-strain) (p for interaction=0.057). When the effect modification by obesity was assessed in men and women separately, there was some evidence for effect modification among women (p for interaction=0.090) but no evidence for an effect modification among men (p for interaction=0.86). The effect of psychosocial work stressors on incident T2DM among obese women (HR 2.81 for iso-strain) was much higher than the effect among lean women (HR 1.54 for iso-strain).

Obese people can be seen as biologically vulnerable as their condition is associated, among other changes, with elevated blood pressure, adverse lipid profile, systemic inflammation and insulin resistance. In addition levels of cortisol, which as described in chapter 1 antagonises insulin, are elevated among obese people. Exposure to psychosocial work stressors, with subsequent psychoneuroendocrine activation and release of cortisol, could potentially further increase these already elevated risk factors and hence the higher effect among the obese. However, no effect of psychosocial work stressors on incident T2DM was observed among obese men, thus raising some questions about the biological

plausibility of this explanation. As discussed in sub-section 10.2.1, there is some evidence for gender differences in psychoneuroendocrine activation and cortisol release. If psychoneuroendocrine activation and release of cortisol and inflammatory markers is more pronounced among women than men, then it could be plausible that any effects of work stressors on T2DM are higher among obese women but not among obese men. Alternatively a social explanation for the effect modification by obesity would be that obese people are facing extra discrimination due to their body weight status making them more vulnerable to other psychosocial insults (i.e. psychosocial work stressors). Such discriminations may be felt more strongly among women than men.

10.3 Impact of psychosocial work stressors on incident type 2 diabetes among women

In sub-section 10.2 the effect of psychosocial work stressors on incident T2DM was discussed. The measures of attributable risk and population attributable risk, collectively referred to as measures of impact, provide an estimation of the burden of disease attributable to a specific exposure. The measure of attributable risk provides an estimation of the excess risk both in absolute (i.e. excess disease cases due to the exposure) and relative (proportion of cases attributed to the exposure) terms among exposed individuals. The population attributable risk provides an estimation of the impact of the exposure in the whole study population.

The current project is the first to estimate measures of impact for psychosocial work stressors in relation to incident T2DM. The estimated excess risk of job strain and iso-strain among exposed participants was calculated to 2.3 T2DM cases per 1000 person-years for (35% of exposed cases) and 3.6 cases per 1000 person-years (44% of exposed cases) respectively (chapter 8, table 8.1). Such estimates should be interpreted with caution in order to avoid confusion. The figure of 44% (attributable fraction for iso-strain) does not imply that 44% of participants who had developed T2DM during follow-up *certainly* developed the disease due to exposure to iso-strain and the remaining 56% *definitely did not* develop the disease due to iso-strain. Rather, this is an approximation

calculated by comparing the rate of T2DM among those exposed to iso-strain to the rate among those not exposed to iso-strain. Obviously, these 2 groups of participants have many other differences in terms of other risk factors, thus the estimated excess risk is just a rough approximation rather than an accurate estimation.

Similarly, the population attributable risk provided an approximation for the impact of psychosocial work stressors in the whole study population. Unlike attributable risk, population attributable risk depends on both the effect of work stressors on incident T2DM *and* the prevalence of the specific work stressor in the study population. In other words two risk factors with an effect of similar magnitude would have different population impacts based on their prevalence in the population. For example, smoking has a very big impact on heart disease, as it is both strongly associated with incident heart disease and is highly prevalent in the population. In contrast, the condition familial hypercholesterolaemia (a genetic disorder characterized by high cholesterol levels) has a strong effect on risk of heart disease but it is so rare in the population (0.2%) that its impact is very low. The prevalence of job strain and iso-strain among Caucasian WII participants free from diabetes at analysis baseline (phase 3) was 24% for men and 32% for women and 12% for men and 15% for women respectively. Psychosocial work stressors are relatively common therefore among participants of the WII study. The population attributable risk for job strain and iso-strain was calculated to be 0.7 cases per 1000 person-years (15% of all cases) and 0.5 cases per 1000 person-years (10% of all cases) respectively (chapter 8, table 8.3).

When compared to the impact of other factors associated with risk of T2DM (health behaviours, obesity, hypertension, hypertriglyceridaemia, low HDL, metabolic syndrome), the impact of work stressors is smaller but still substantial (chapter 8, table 8.3). However, when exposure to iso-strain was co-occurring with exposure to other factors (unhealthy behaviours; obesity; metabolic syndrome) there was no substantial excess risk attributed to iso-strain. For example, being exposed to iso-strain resulted in a further 15% excess T2DM cases on top of exposure to unhealthy behaviours, 8% on top of exposure to obesity and 4% on top of exposure to the metabolic syndrome. This

suggests therefore that, in terms of public health impact and policy, preventing iso-strain on top of conventional T2DM risk factors would not further benefit population health in terms of diabetes. This is however not an unexpected finding as obesity and the metabolic syndrome are so strongly linked to T2DM and their prevalence is so high in the population, that alleviating these two exposures, would result in a huge decrease in the burden of diabetes.

Again, it should be stressed that the estimates of population impact presented in chapter 8 and discussed here, are not very accurate and are based on an important assumption, that of a causal association between exposure and outcome. Causality in the relationship between psychosocial work stressors and incident T2DM was discussed in sub-section 10.2.2.2. Even though there was a strong case for a causal association, a possible involvement of reverse causality in the results could not be excluded. Also, these estimates, even though similar to estimates on the impact of psychosocial work stressors on heart disease and depression observed in other studies cannot be generalised and applied for other populations. These estimates are specific for the Caucasian female population of the WII study who was free from diabetes at phase 3 (1991-93). Other populations may have a different prevalence of these work stressors and therefore the population impact would be different. If however the prevalence of job strain and or iso-strain was known among women in the general population, the population impact could be calculated using the effect estimates from the current results. Still, this would not be very representative as the sample of women in the WII study are not a representative sample of women from the general population. The issue of generalizability of results is discussed in sub-section 10.6.2.1.

10.4 Pathways between psychosocial work stressors and type 2 diabetes

Potential pathways in the association between psychosocial work stressors and T2DM were investigated in chapter 9. The hypothesized pathways were described in detail in chapters 1 and 2 and are graphically displayed in figure 2.1. Broadly, these pathways can be grouped into indirect (through health behaviours) and direct (through obesity and

cardiometabolic and inflammatory risk factors). Evidence from the literature review conducted in the current project (chapter 2) was inconclusive for the potential of these hypothesized mechanisms to mediate the association between psychosocial work stressors and T2DM, mostly because of mixed evidence on the association between work stressors and key mediators in the causal pathway.

In the this project, evidence for mediation of the effect of psychosocial work stressors on incident T2DM among women was restricted to just a few biological risk factors. The main mediator was obesity (BMI) explaining ~15% of the effect. Inclusion of HDL-cholesterol in the explanatory model increased the mediation to ~20% and further addition of inflammatory markers resulted in an overall mediation of ~30%. Addition of blood pressure did not provide further mediation. This may suggest that even though acute psychosocial stressors have been shown to increase blood pressure, this does not lead to chronic substantial elevations in blood pressure, which would contribute to the development of T2DM. The proposed indirect pathway is, however, the one that lacks support from the findings of this project. Psychosocial work stressors were not linked to health behaviours among women (chapter 9) and hence the lack of mediation. This section of the discussion will therefore concentrate on 3 issues:

1. How do the identified mechanisms linking psychosocial work stressors to T2DM operate?
2. Why the proposed plausible mechanisms explain only a part of the effect of psychosocial work stressors on T2DM?
3. What mechanisms could explain the remaining effect of psychosocial work stressors on T2DM after adjustments for potential confounders and mediators?

10.4.1 How do the identified mechanisms linking psychosocial work stressors to T2DM operate?

Health behaviours explained 7% of the effect of iso-strain on incident T2DM. This is a small proportion of effect explained, given the detailed description of the potential mechanisms linking psychosocial stressors to cardiometabolic disease risk through health behaviours (Siegrist, 1998; Dallman et al, 2007) (chapter 1). Due to the small extent of mediation these behavioural pathways will not be discussed in this chapter, which will concentrate on direct biological mechanisms.

10.4.1.1 Pathway through obesity

Obesity is recognised as the most important risk factor for T2DM (Guh et al, 2009). Baseline BMI explained 14% of the effect of iso-strain on incident T2DM. Measures of central obesity explained a smaller proportion of the effect compared to BMI. The explained effect was 4% for waist circumference and 9% for waist-height ratio. This indicates that the hypothesis that exposure to psychosocial stressors increases central rather than general obesity (Steptoe & Wardle, 2005; Dallman, 2007) is not supported by evidence from the current project. In the WII study exposure to iso-strain has been linked prospectively to both central and general obesity (Brunner et al, 2007).

Chronic exposure to psychosocial stressors with subsequent activation of the HPA axis results in elevations of cortisol. A state of chronically elevated cortisol, usually termed hypocortisolaemia, can alter metabolism and in particular the mechanisms and rate by which the body mobilizes and stores body fat, shifting the balance towards storing of energy in the form of adipose tissue (Bjontorp & Rosmont, 2000; Pasquali et al, 2006). The gradual accumulation of body fat eventually leads to a decrease in insulin sensitivity, mainly through the action of non-esterified fatty acids (NEFA) and eventually to T2DM.

10.4.1.2 Pathway through HDL

HDL-cholesterol levels are lower than normal in patients with T2DM and among such patients, the more severe the hyperinsulinaemia, the lower the HDL levels (Chen et al, 1987). Low HDL-cholesterol has been also known to precede the development of T2DM. In the current project, baseline HDL-cholesterol levels explained 5% of the effect of psychosocial work stressors on incident T2DM no top of differences in BMI. This is a small additional mediation, thus the pathway through HDL-cholesterol will be discussed only briefly.

As described in chapter 1 of this thesis, activation of the central nervous system via chronic activation of the acute stress response results in elevations of blood triglyceride levels due to mobilization of body fat stores. Chronically elevated triglyceride levels in turn result to triglyceride enrichment of HDL particles. This enrichment is a result of the activation of hepatic lipase (lipid breaking enzyme) which aids the exchange of triglycerides and cholesteryl esters between HDL and triglyceride-rich lipoproteins (Rashid et al, 2003). HDL-cholesterol removes free cholesterol from peripheral tissues. High concentrations of plasma cholesterol levels and in particular high concentrations in the pancreas may contribute to dysfunction of pancreatic cells responsible for the production of insulin. This eventually leads to loss of insulin secretion and T2DM (Brunham et al, 2008).

10.4.1.3 Pathway through low grade inflammation

Inflammatory markers, such as fibrinogen, CRP and IL-6 are gaining attention as novel markers of T2DM risk. In the current project, baseline inflammatory markers (fibrinogen, CRP, IL-6, vWf, factor VII) explained an extra 14% of the effect of psychosocial work stressors on incident T2DM on top of BMI and HDL-cholesterol.

There are several mechanisms that might contribute to acute changes in circulating levels of inflammatory markers in response to psychosocial stress. The rise in circulating levels of inflammatory markers following acute psychosocial stress is due to *de novo* synthesis,

as well as increases in the number of cytokine-synthesizing cells contributing to circulatory levels (Steptoe et al, 2007). Stressor-induced inflammatory responses favour a catabolic state and suppress anabolic pathways, such as the insulin signalling pathway. Insulin affects cells through binding to its receptor on the surface of insulin-responsive cells. This binding initiates downstream signalling events, which initiate a cascade of events for the uptake and utilization of blood glucose from tissues. Low grade inflammation can inhibit this signalling and this is a primary mechanism through which inflammation leads to insulin resistance and T2DM (Wellen & Hotamisligil, 2005).

10.4.2 Why the proposed plausible mechanisms explain only a part of the effect of psychosocial work stressors on T2DM?

The mechanisms linking psychosocial work stressors to T2DM have been described in detail in chapter 1. These mechanisms are widely recognised as the most biologically plausible mechanisms linking psychosocial stressors to cardiometabolic disease in general (Brunner, 1997; McEwan, 1998, Strike & Steptoe, 2004, Brotman et al, 2007; Eller et al, 2009). The literature review from epidemiological studies on these pathways, presented in the current thesis (chapter 2), showed that evidence linking psychosocial work stressors (which have been shown to increase risk of CVD) to behavioural and biological risk factors was inconsistent. Results from the current project (chapter 9) confirm that the mediating role of the proposed biological (obesity, blood pressure, blood lipids, inflammation) and especially behavioural (diet, physical activity, alcohol consumption, smoking) is not as strong as expected. The possible explanations for this discrepancy between hypothesized pathways and empirical evidence, with a special emphasis on the role of indirect pathways (on which no evidence of mediation was found) will be discussed in the current sub-section. The main issues addressed are: (i) Whether the proposed plausible mechanisms in the literature were not based on empirical observations on physiological responses to stressor exposure; and (ii) whether the proposed plausible mechanisms linking psychosocial stressors to T2DM are not activated from exposure to *work-related* psychosocial stressors.

10.4.2.1 Are the proposed plausible mechanisms linking psychosocial stressors to cardiometabolic risk backed by empirical observations?

The biological mechanisms linking psychosocial stressors to cardiometabolic disease have been proposed by several research groups during the last 20 years (Karasek & Theorell, 1990; Siegrist, 1995; Brunner, 1997, McEwan, 1998, Belkic et al, 2004, Brotman et al, 2007; Eller et al, 2009). Four high-quality reviews, give a detailed account of these mechanisms, and all agree that empirical evidence is needed to confirm the hypothesized pathways (Hemingway & Marmot, 1999; Belkic et al, 2004; Brotman et al, 2007; Eller et al, 2009). The behavioural mechanisms received detailed attention during the last decade, with researchers proposing that exposure to psychosocial stressors increases salience to unhealthier behaviours and hence chronic disease (McEwan, 1998; Siegrist, 1998; Dallman et al, 2003).

Empirical evidence on the biological mechanisms linking psychosocial stressors to psychoneuroendocrine responses and pathophysiological changes is given in sub-section 10.2.1.2.1 in the current chapter. For example, individuals reporting low job control had greater fibrinogen responses to acute stress than did those with high job control (Steptoe et al, 2003). Overcommitment at work (ERI model) was associated with elevated cortisol levels and systolic blood pressure (Steptoe et al, 2004) as was job strain among a sample of teachers (Steptoe et al, 1999). Therefore, the biological pathways hypothesized initially by physicians and then adopted by health researchers are supported by a large body of evidence from both human and animal experimental studies. Stressors in the workplace have been shown to activate the acute stress response and to cause pathophysiological changes in the body. Evidence on the indirect pathway is discussed in more detail below.

Evidence on the indirect (behavioural) pathway from studies on humans is concentrated mainly on food choice. Affect asymmetry, whereby negative affects dominate peoples experience and likely to be linked to exposure to psychosocial stressors, was found to predict high fat/high sugar food consumption in normal weight individuals (Dube et al, 2005). The authors found that consumption of such foods alleviated women's negative

emotions. Such associations were not observed in men. High cortisol reactivity in response to stress was found to lead to stress-related overeating and high fat/high sugar food consumption in 59 healthy pre-menopausal women (Epel et al, 2001). In a study among 46 binge eating college women who kept daily diaries for 30 days, higher stress was associated with increased risk of same-day binge eating, while social support was associated with decreased risk of same-day binge eating (Freeman & Gil, 2004). In two intervention studies aiming to investigate the effect of psychosocial stress on food choice, participants who had to prepare a 4-minute speech, expecting it to be filmed and assessed (Oliver et al, 2000) and participants given ten unsolvable five-letter anagrams (Zellner et al, 2006), showed increased consumption of high fat/high sugar foods and avoided healthier options (i.e. grapes) compared to the control groups.

The above evidence highlights that in periods of acute stress people tend to adhere to unhealthier behaviours, especially related to food choice. The proposed mechanisms involve activation of the dopamine reward system, as well as elevations in serotonin levels as a result of certain unhealthy behaviours, such as high fat/high sugar foods, alcohol consumption and smoking. The proposed indirect pathway linking psychosocial stressors to cardiometabolic disease was mainly proposed from such observations. However, exposure to acute and chronic stressors is very different. Even if the proposed mechanisms (through brain neurotransmitters) do operate, there are many other factors determining health behaviours. Despite biological mechanisms, which are more 'automated', health behaviours could be altered by cognitive effort. For example, a person may stop his/her urge of eating unhealthily when stressed, as a means of preventing weight gain. On the same lines, someone could stop his/her urge of consuming alcohol or smoking when stressed for a series of reasons. Therefore, even though exposure to acute stressors is followed by acute change in behaviour, exposure to chronic stressors (i.e. work stressors) is less likely to be accompanied by chronic alterations in health behaviours. In fact, this is supported by both the literature review (chapter 2) and the current results (chapter 9) showing a weak and inconsistent association between work stressors and health behaviours. Blane (2006) summarizes evidence on the role of psychosocial factors across the life-course in relation to health behaviours and suggests

that evidence supports that these are more influenced by childhood rather than adult psychosocial circumstances.

In summary, it can be concluded that the proposed plausible *direct* mechanisms linking psychosocial work stressors to T2DM are backed by evidence from empirical observations of activation of the central nervous system and the related psychoneuroendocrine responses of the acute stress response. The *indirect* mechanisms however, rely mostly on theories rather than empirical observations and are not backed by evidence on the effects of *chronic* exposure to psychosocial stressors on health behaviours.

10.4.3 Plausible mechanisms explaining the remaining effect of psychosocial work stressors on T2DM after adjustments for confounders and mediators

The results of the current project support that just over 30% of the effect of iso-strain on incident T2DM was explained by obesity, HDL-cholesterol and inflammatory markers. What about the remaining 70% then? It should be noted here that the proposed plausible mechanisms investigated in the current project, were ‘borrowed’ from research on the involvement of psychosocial stressors in heart disease. This may provide an explanation for the relatively low observed mediation. However, these cardiometabolic risk factors also explained only 1/3 of the association between iso-strain and heart disease (Chandola et al, 2008). That analysis by Chandola et al (2008) did not include markers of inflammation in the analysis, thus the proportion of effect explained is likely to have been higher if such risk factors were included. In general, in epidemiological studies, explaining 1/3 of an association through adjustment for potential mediators is considered a relatively high mediation, given the methodological limitations of observational studies, especially when these rely to self-reported measures. A reason for this is the contribution of several (sometimes unknown or unmeasured) factors in the development of chronic diseases. Also, inaccurate assessment of potential mediators can result in these mediators not ‘explaining’ the full proportion that they could have ‘explained’ if assessed accurately.

The current project aimed at investigating the *major* proposed mechanisms linking work stressors to T2DM. Below, some additional mechanisms will be proposed, which may be more relevant to T2DM than other cardiometabolic diseases.

10.4.3.1 Biomarkers in the direct psychoneuroendocrine pathway

Despite sharing of common risk factors with CVD, T2DM is a different condition which may be more sensitive to other biological insults. For example, it can be speculated that the mechanisms linking psychosocial work stressors on T2DM may be ‘more direct’ than for heart disease. In other words, stressor-induced activation of the sympathetic nervous system, with activation of the HPA axis could directly increase T2DM risk, without increases in cardiometabolic risk factors such as blood pressure and cholesterol.

10.4.3.1.1 Direct effects of cortisol

A strong candidate for these direct effects of psychosocial stressors on T2DM development is cortisol. This stress hormone has been extensively mentioned throughout this thesis and its involvement in the stress response was discussed in detail in chapter 1 as well as in the current chapter. Chronic elevations in cortisol, due to prolonged and repeated activation of the HPA axis, are detrimental in proper metabolic functioning. Cortisol, being a catabolic hormone, interferes with the proper functioning of insulin (an anabolic hormone) by counteracting its actions. Cortisol promotes the breakdown of lipids and proteins to provide substrates for increasing gluconeogenesis in the liver. This leads to increased blood glucose concentrations (through gluconeogenesis). Therefore, any elevations in cortisol result in hyperglycaemia and consequently hyperinsulinaemia, as the body strives to compensate with the elevated blood glucose levels. In addition, cortisol interferes with the proper functioning of insulin by reducing insulin sensitivity in tissues. Therefore, cortisol has a dual action, first by elevating blood glucose and hence insulin levels (resulting in hyperglycaemia and hyperinsulinaemia) and then by reducing the action of the elevated insulin through decreases in insulin sensitivity. The result of this dual action is insulin resistance and eventually T2DM.

As discussed in sub-section 10.4.3.2 of the current chapter, there is evidence in the literature for an elevation of cortisol levels among individuals exposed to psychosocial work stressors (Chida & Steptoe, 2009; Chandola et al, 2008). In experimental studies aiming to investigate psychoneuroendocrine pathways in the development of T2DM, participants who had a flat, rigid day curve and poor feedback mechanism of cortisol also had insulin resistance and hyperglycaemia (Bjontrop et al, 1999; Rosmond & Bjontrop, 2000). In a case-control analysis from the WII study, participants with the metabolic syndrome (cases) had higher levels of cortisol metabolites compared to controls and job strain accounted for around 10% of this effect (Brunner et al, 2002). In other words, there was evidence that 10% of the higher levels of cortisol among participants with the metabolic syndrome was explained by the higher prevalence of job strain among those participants. The metabolic syndrome is a major risk factor for T2DM (*Smith, 2007*) so the particular analysis provides evidence supporting a potential causal role for cortisol in the iso-strain-T2DM association. In an experimental study looking at the effect of anticipation to surgery (a stressor) on insulin resistance, serum cortisol levels were the best predictor (Lehrke et al, 2008). As already mentioned, patients with Subclinical Cushing's syndrome, which is characterized by chronic elevations in cortisol, also show signs of insulin resistance and are at an increased risk of T2DM (Tauchmanova et al, 2002).

10.4.3.1.2 Potential mechanism through non-esterified fatty acids

Another mechanism through which psychosocial stressors could increase risk of T2DM is elevations in concentrations of non-esterified fatty acids (NEFA), also called free fatty acids. Activation of the acute stress response, with release of catecholamines and glucocorticoids, increases lipolysis. As a result triacylglycerol (body fat molecule) breaks down into glycerol and NEFA. Chronic activation of the acute stress response could therefore result in chronically elevated NEFA concentrations. Prolonged exposure of the pancreas to NEFA impairs β -cell function, thus impairing secretion of insulin and increasing the risk of T2DM (Kashyap et al, 2003).

10.4.3.1.3 Potential mechanism through adipokines

Adipokines are cytokines secreted by adipose tissue. Leptin is an adipokine which plays a key role in metabolism by regulating energy intake and energy expenditure. Leptin has been shown to improve insulin secretion and sensitivity (Wauters et al, 2003). A condition referred to as leptin resistance is characterised by a diminished capacity of leptin to exert its actions. Therefore leptin resistance could potentially contribute to insulin resistance and risk of T2DM (Abdella et al, 2005). Another adipokine, adiponectin modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin also has important endogenous anti-inflammatory role thus decreases in adiponectin could increase the risk of T2DM (Tsatsanis et al, 2006). Concentrations of leptin and adiponectin did not predict weight gain and BMI in the Rancho Bernardo cohort (Langenberg et al, 2005) indicating that any effects on T2DM risk are probably not through adiposity.

Increased levels of glucocorticoids are reportedly capable of stimulating the synthesis and secretion of leptin (Newcomer et al, 1998). It has been recently suggested that the elevations in glucocorticoids can induce leptin resistance (Otsuka et al, 2000; Pickup, 2000). In addition activation of the stress response has been linked to reduction of adiponectin levels (Shiolah, 2007).

In an epidemiological study among Japanese employees work-related perceived psychosocial stress was related to higher leptin concentrations, probably indicating leptin resistance (Otsuka et al, 2000). In a small-scale study investigating the role of leptin in the acute stress response and as a mediator of stress-induced diabetes, serum leptin increased at a higher extent among diabetic patients who were identified as high acute-phase responders. The authors concluded that elevated leptin concentrations in T2DM are partly related to chronically activated acute phase stress response, which is independent of BMI (Pickup, 2000). Shiolah et al (2007) showed that psychotic (not psychosocial) stress was associated with lower adiponectin levels and a dose-response way. Also, experimental studies looking at the effect of exposure to a psychological stressor (anticipation to surgery) on levels of adipokines, consistently show an increase in the

levels of leptin and a decrease in the levels of adiponectin (Lehrke et al, 2008; Hernández et al, 2000).

10.4.3.1.4 Potential mechanism through Neuropeptide Y

Neuropeptide Y (NPY) is a neurotransmitter found in the brain and autonomic nervous system. NPY is involved in the regulation of energy balance, with its main effect being to increase energy intake and decrease energy expenditure. NPY is secreted by the hypothalamus and, in addition to increasing food intake, it increases the proportion of energy stored as body fat. High levels of glucocorticoids stimulate release of NPY from sympathetic nerves, which in turn upregulate NPY and its receptors in the abdominal fat. This leads to accumulation of abdominal fat which is strongly linked to insulin resistance and T2DM (Kuo et al, 2077)

10.4.3.2 Alternative pathway through sleep disturbances

Throughout this thesis the hypothetical plausible pathways linking psychosocial work stressors to T2DM, as proposed in the literature (Brunner, 1997; McEwan, 1998; Brotman et al, 2007), have been grouped into indirect behavioural and direct biological. However, a third (indirect) pathway, much less investigated, may be operating through disturbances in sleep, resulting from chronic exposure to psychosocial work stressors.

Although viewed as a passive condition, sleep is a highly active and dynamic process. Until recently, it was believed that sleep was important primarily for restoring brain functions. However, there is increasing evidence that sleep also modulates the metabolic, endocrine and cardiovascular systems (Trenell et al, 2007). The pathways involved therefore are similar to those of exposure to psychosocial stressors, as sleep disturbances activate the sympathetic nervous system and the HPA axis. The proposed mechanisms linking sleep disturbances to T2DM involve accelerated accumulation of visceral fat, elevations in cortisol and leptin and direct impairment of insulin sensitivity (McEwan, 2006; Martins et al, 2008). In experimental studies, sleep deprivation causes substantial increases in blood glucose and insulin during the day. Three recent reviews summarising

evidence from small-scale experimental and larger epidemiological studies, concluded that there is growing evidence supporting an independent role of sleep quality in the pathogenesis of T2DM (Schultes et al, 2005; Spiegel et al, 2005; Martins et al, 2008).

Psychosocial work stressors have been shown to increase sleep disturbances (Karasek & Theorell, 1990; Kim & Dimsdale, 2006; Akerstedt, 2007; Nakata et al, 2008). Some of the potential direct effects through cortisol and leptin described in sub-section 10.4.4.1.3 could be mediated by sleep disturbances. This could be therefore an alternative pathway through which psychosocial work stressors could increase risk of T2DM. It should be noted that evidence shows that women have a greater prevalence of insomnia and are reporting lower subjective sleep quality compared to men, irrespective of age (Trenell et al, 2007). This therefore could potentially explain some of the gender differences in the effect of psychosocial work stressors on incident T2DM.

10.5 Strengths and limitations of the current research project

10.5.1 Project strengths

10.5.1.1 Project setting and quality of data

Whitehall II is unique in that it was the first study explicitly set up to determine the extent by which psychosocial factors at work influence disease outcomes. The Whitehall II study has a large sample size (N=10 308) comprising of both male and female civil servants working in 5766 different jobs, providing thus excellent opportunities for assessing a variety of psychosocial work stressors. The WII dataset can address a major issue in contemporary epidemiology; that risk factors and determinants operate at layers from social determinants, to psychosocial factors in the work and outside, to health behaviours, to biomarkers of disease risk.

The high quality of the data available in the WII study is also among the strength of the current project. Psychosocial work stressors were assessed based on the 2 main models of work stress, namely the demand/control/support model and the effort-reward-imbalance

model. Even though the scales were not used in their original form, the derived variables of job strain, iso-strain and ERI have shown high validity and reliability (see methods chapter) and were associated with several disease outcomes from minor psychiatric disorder (Stansfeld et al, 1995) and cognitive decline (Elovainio et al, 2009), to obesity (Brunner et al, 2007), to heart disease and the metabolic syndrome (Chandola et al, 2006; Chandola et al, 2008).

The WII study also provided good quality data for the outcome of interest of the current project. The study is among the few in the world to have repeated clinical ascertainment of T2DM, with an oral glucose tolerance test. For the current project, which used data up to phase 7 (2002-04), 3 waves of clinical assessment of T2DM were used. Exclusion of prevalent cases at the beginning of follow-up and identification of incident cases during follow-up based on accurate ascertainment, are vital in reducing bias from the results. The long follow-up (15 years for the main analysis) also provided a suitable setting for investigation of the temporal sequence of the association between the work stressors and T2DM.

In addition, the WII study has quality data on the main confounding and mediating factors relevant to the current project. Civil service employment grade is an accurate measure of SEP. Outside work psychosocial stressors and psychological traits were also available. Health behaviours assessed included detailed assessment of diet with a FFQ, of physical activity by deriving a MET-score, as well as of alcohol consumption and smoking. Biological factors were also available in abundance, with accurate measurements of, among others, anthropometric factors (weight, height, waist and hip circumferences), blood lipid profile (blood cholesterol and triglycerides), blood pressure and several inflammatory markers (fibrinogen, CRP, IL-6 and others.).

The WII study therefore provided an excellent setting for the investigation of the association between psychosocial work stressors and incident T2DM and the pathways involved. The detailed assessment of the main exposures and outcome of interest, the availability of several potential confounding factors and the prospective nature of data

collection in the WII study helped in calculating accurate estimates for the association between work stressors and T2DM risk.

10.5.2 Project limitations

10.5.2.1 Self-reported nature of exposure

The exposure of interest of the current project, psychosocial work stressors, was based on self-reports. Participants reported a series of psychosocial work characteristics, which should hypothetically capture characteristics of the working environment which have the potential to generate psychosocial stress, hence the name psychosocial work stressors. However, subjective reporting of these characteristics may be biased by the general psychological state of the participant during the recent past prior to questionnaire completion or indeed may reflect a stressful or unpleasant day at work the day before questionnaire completion. Such information bias may result in reduction of the effect towards null (if random) leading to type II errors, or could introduce the phenomenon of reverse causality, where the outcome causes the exposure instead of vice versa. In other words a type I error. Several steps were taken in the analysis in order to reduce the possibility of such phenomena. These are discussed in detail in sub-section 10.2.2.1.2.

Objective measures of psychosocial work stressors would as well be somewhat problematic and difficult to assess. The hindrance/utilization model is a model of objective psychosocial stress. When this was compared to the demand/control/support and ERI models results showed that the demand/control/support model explained the most variance in depression and anxiety symptoms (Griffin et al, 2007). In addition, the experience of perception of a psychosocial stressor is somewhat personal. For example two people may appear to be exposed to similar (adverse) working conditions. One of the two may feel that he/she is affected by this and reports a 5, for example, in the Likert scale. The other does not feel that is affected by this and reports a 2, for example, in the scale. Objectively, these 2 individuals are exposed to the same stressor. Subjectively however, only the latter is exposed to a stressor, as for the former the exposure (whatever that is) is not a stressor. Therefore self-reported models of work stressors can be regarded

as a combination of objective and subjective measures of stress. Indeed, these psychosocial work stressors (job strain, iso-strain and ERI) have been linked to several disease outcomes in many studies around the world (Belkic et al, 2004; Siegrist, 2005) thus proving that the validity of the measures in capturing adverse psychosocial work experiences is adequate.

10.5.2.2 Generalizability of findings

Participants of the WII study are not a representative sample of the general population. The study sample only includes non-manual occupations and women are underrepresented. The specific sample used for the current analysis is even less representative as due to several exclusions, more socially advantaged participants were included for analysis (mainly due to missing data among lower employment grades). Also, ethnic minority groups were excluded from analysis. Therefore, the results of the study provide evidence for an effect of work stressors on T2DM risk among Caucasian women working in non-manual occupations in the UK society. Further generalizations based on the current findings should be avoided.

Although, working conditions in the WII study are perhaps among the better regulated in the working population, it is likely that work stressors are much higher in the general working population. Therefore, the prevalence of psychosocial stress at work in the general working population is likely to be underestimated, which may also result in an underestimation in the effect and impact of psychosocial work stressors on T2DM in the general population. Also, the associations between work stressors and disease in the current study may underestimate the effect of work stressors on type 2 diabetes in the general female working population.

10.5.2.3 Low study power for assessing certain associations within sub-groups

A limitation of the current project is the low study power for investigating certain associations. Among the objectives of the current project was to investigate effect modification in the association between work stressors and incident T2DM. In order to do

this, analysis had to be carried out stratifying by the potential effect modifiers (age, employment grade and obesity). The sample of women in the high employment grade was relatively small however, as was the sample of men and women in the low grade. Among women, stratifying by age and obesity also resulted in low power in the analysis. Due to this, it was not possible to estimate with certainty the stratified effect of work stressors on incident T2DM and to assess evidence on interaction among women.

10.6 Implications for research

10.6.1 Observational studies

The findings of this project extend the evidence from previous studies on the role of psychosocial work stressors in the development of T2DM. The gender difference in the effect of work stressors, consistently observed in the literature, should be further investigated by analyses specifically aiming at elucidating gender differences in the plausible pathways linking work stressors to T2DM. For example a study could aim to investigate gender differences in psychoneuroendocrine activation during the working day, with accurate measurements of biomarkers of psychosocial stress, such as cortisol, and catecholamines, as well as heart rate variability. Gender differences in psychoneuroendocrine activation among men and women reporting exposure to psychosocial work stressors would also help in elucidating differences in disease risk between the two genders.

The effect modification by SEP and body weight status, observed in the current results, should be further investigated and confirmed by other studies to examine whether this is a cohort-specific observation or whether it applies to other populations as well. No study has before investigated either of these two effect modifications but, based on these results, these interactions should not be ignored by future studies as they may provide further insight into specific groups of individuals who are particularly vulnerable to the effects of psychosocial work stressors on disease risk.

The impact of psychosocial work stressors on T2DM should also be investigated in other populations to ascertain whether the burden of exposure to such stressors differs in different countries and populations. As previously described, the population impact of an exposure on a disease depends on the prevalence of that exposure in a given population. Therefore, investigation of impact in different studies around the world could help identify a range of values for the impact of psychosocial work stressors on T2DM. In addition, this would help avoid unnecessary generalizations on population impact based on a limited number of studies from very specific populations.

This project investigated the main proposed pathways linking psychosocial stressors to T2DM. Investigation of other plausible pathways, proposed in sub-section 10.4.3, would elucidate further the mechanisms linking psychosocial stressors to T2DM, thus strengthening the case for a causal association. However, only a few studies have detailed data on psychosocial work stressors *and* incident T2DM *and* potential mediators (cardiometabolic, inflammatory and other novel risk markers). There is a need for studies specifically designed for investigating mechanisms linking psychosocial stressors to incident disease. As it would be too costly to design a large-scale study with detailed assessment for all the above factors, sample size could be sacrificed for the detail and sophistication of data collection on the main exposures and outcome and potential confounders and mediators. For example, obesity, a main mediator in the given association, could be assessed by detailed techniques such as computed tomography, dual-energy x-ray absorptiometry and ultrasound. Such techniques have the ability to accurately quantify abdominal body fat, which is hypothesized to be directly linked to raised cortisol levels resulting from exposure to psychosocial stressors.

Studies looking at the effect of psychosocial work stressors on blood glucose and insulin levels, as well as measures of insulin resistance and sensitivity (i.e. HOMA-IR) would be extremely useful in confirming the results of studies looking at incident diabetes as the outcome. The design of such studies should preferably be prospective as it would be hard to exclude reverse causality in cross-sectional analysis on the specific association.

Unfortunately only a few studies worldwide have repeated measures of clinically assessed blood glucose and insulin and measures of insulin sensitivity.

10.6.2 Intervention studies

All the evidence on the effect of psychosocial work stressors on T2DM (including the current project), as well as cardiometabolic disease in general (heart disease, obesity, the metabolic syndrome) comes from observational epidemiological studies. Such studies may have the benefit of relatively easy data collection and long follow-up periods (in the case of cohort studies), but lack the experimental design of intervention studies, which, as previously mentioned, provide the strongest case for a causal association.

The above drawback of observational studies applies even more for psychosocial work stressors, which rely on self-reports with a considerable risk of information bias. In addition, the biological plausibility of the effect of such work stressors on disease has yet to be established. A good example highlighting the importance of intervention studies for generating evidence on epidemiological associations are the contrasting evidence generated from observational and intervention studies on the association between beta-carotene intake and cardiovascular mortality. Observational studies show considerable benefit, whereas the findings from randomised controlled trials show an increase in the risk of death (meta-analysed results) (Lawlor et al, 2004). Given this, intervention studies would greatly benefit the field of psychosocial determinants of T2DM and cardiometabolic disease in general.

The problem with intervention studies in the case of the given association is that it would be unethical to induce chronic psychosocial stress on people in an experimental fashion. What could however be done experimentally is removal or reduction of exposure to psychosocial stressors. In fact, a few studies have investigated the association between psychosocial work stressors and morbidity in the workplace, using an experimental design. Findings from such studies are promising.

In a stress prevention trial among bus drivers, an intervention included relaxation; coping with anger and excessive work commitment (high need for control); management of conflicts with superiors; and recommendations for structural changes at work, resulted in a reduction in 'need for control' in the intervention group (Aust et al, 1997). In a study involving reduction of objective workload levels among UK driving examiners, reduced workload among the intervention group resulted in an increase in job satisfaction, reductions in anxiety and lowered heart rate (Parkes et al, 1986; Parkes, 1995). In a Dutch study among driving examiners randomised into 3 groups differing in working conditions over three weeks, those in the less intense work environment had higher mental efficiency, lower adrenalin levels, better sleep quality and no carry-over effect of evening tension in the following morning compared to those in the less intensive schedules (Meijman et al, 1992).

Such intervention studies would be even more informative if they included cardiometabolic outcomes, such as blood glucose and insulin levels, as well as blood lipids, blood pressure and markers of inflammation. For example it would be interesting to investigate the prospective effect of a long-term intervention programme aimed at reducing psychosocial work stress on cardiometabolic outcomes such as blood glucose and lipids, hypertension and low-grade inflammation.

In the following sub-section, implications for policy are discussed based on the findings of this research project.

10.7 Implications for policy

This section of the thesis concentrates on primary prevention. In other words, how incidence of T2DM could be reduced through reductions in workplace stress among healthy individuals. The effect of psychosocial work stressors was stronger and more consistent among women and among individuals in the lower civil service employment grades and obese individuals. Implications for policy will be discussed in general however because: (i) more evidence supporting these gender differences and effect

modifications on T2DM risk is needed; and (ii) even if such observations are confirmed by other studies it would not be justified to apply policies based on one health outcome (T2DM). For example, exposure to work stressors has been linked to heart disease among men (Belkic et al, 2004).

This project was not directed towards occupational health and worksite health promotion, so implications will not be discussed in great detail. Three levels were identified for potential intervention: (i) the societal level; (ii) the worksite level; and (iii) the individual level.

10.7.1 Policy implications at the societal level

Psychosocial factors themselves are determined largely by social, political, and economic factors. Primary prevention at the societal level mainly involves governmental initiatives for reducing work-related stress among employees through a reduction of exposure to psychosocial work stressors. Interventions at the societal level are a responsibility of governments through initiation and funding of governmental bodies aiming at campaigning for the reduction of work-related stress.

The Health and Safety Executive (HSE) is a non-departmental public body which aims at preventing death, injury and ill-health to those at work and those affected by work activities. Among other work-related issues, the HSE aim at reducing exposure to psychosocial work stressors. In their website (<http://www.hse.gov.uk/stress>) they provide information on the following: (i) Information on work related stress; (ii) advice on ways to deal with work stress; and (iii) information on how work organisations could tackle work related stress. The final point is of special importance and is labelled as ‘The Management Standards for work-related stress’. The Management Standards define the characteristics, or culture, of an organisation where the risks from work-related stress are being effectively managed and controlled. The Management Standards cover six key areas of work design:

- Demands: including guidelines on workload, work patterns and the work environment.
- Control: including guidelines on how much say the person has in the way they do their work.
- Support: including guidelines on the encouragement, sponsorship and resources provided by the organisation, line management and colleagues.
- Relationships: including guidelines on promoting positive working to avoid conflict and dealing with unacceptable behaviour.
- Role: including guidelines on helping employees understand their role within the organisation and whether the organisation ensures that they do not have conflicting roles.
- Change: including guidelines on organisational change is managed and communicated in the organisation.

This initiative is aiming to tackle the exact problem that the current project addresses. In fact, reduction of the main components of the iso-strain model of work stress (high demands/low control/low work social support) is among the aims of the Executive. What is lacking however is engagement of the public in this body.

‘Health, Work and Well-being’ is another government-led initiative aiming to improve the health and wellbeing of working age people. An important initiative of ‘Health, Work and Well-being’ is to support and summarize evidence from case studies on how different organisations have implemented and benefited from innovative health and wellbeing initiatives in the workplace. A good example of such a case study (www.workingforhealth.gov.uk/Case-Studies) which involved reduction of work-related stress is the ‘cultures and values’ programme implicated at Bradford & Bingley, which included initiatives for the development of a stress management programme for all staff, including a counselling service for staff to discuss work and personal matters and an occupational therapist advice. These initiatives resulted in a reduction in staff turnover from 30% in 2005 to 23% in 2006; improvement of job satisfaction among employees (proportion recommending Bradford & Bingley as a place to work increased from 45% in

2005 to 72% in 2006); a decrease in the prevalence of smoking among employees; an increase in the proportion of employees taken up pilates and purchasing bicycles; and a reduction of work stress-related absence by 80%.

In 2007, the UK Health Minister, Ivan Lewis, announced £20 million of capital funding to finance new NHS Plus demonstration sites to help improve the occupational healthcare services offered to small and medium sized businesses. The NHS Plus aims to “tackle the work-related health problems suffered by employees and help them to get back to work” (www.workingforhealth.org.uk).

Therefore the need for intervening for reducing exposure to psychosocial work stressors at the societal level has been identified and well discussed. Despite beneficial indications from case studies, implementations of recommendations and assessment of the effects of intervention programmes are still at a very early stage. The government should support and fund advertising of the website ‘www.hse.gov’ and ‘www.workingforhealth.org.uk’ and make citizens more aware of the hazards related to exposure to work stressors.

10.7.2 Policy implications at the worksite level

Policy implications at the worksite are those more relevant for the current project. Interventions aiming to tackle issues at the worksite level are usually referred to as organizational or structural interventions. In a review by Parkes and Sparkes (1998), worksite interventions for reducing work-related stress were divided into: (i) socio-technical; and (ii) psychosocial. This sub-section discusses potential implications based on these two categories of intervention.

10.7.2.1 Socio-technical interventions

According to Parkes and Sparkes (1998) socio-technical interventions, in general, involve improvement of work schedules and an overall reduction in workload as a means of reducing exposure to work stressors.

For a reduction in high job demands, supervisors should be encouraged to identify jobs characterised by high working pace and intensity and withdraw some tasks or be more flexible on deadlines. In particular supervisors should avoid exposing employees to conflicting demands.

For a reduction in low job control, supervisors should be encouraged to enable as much involvement for employees in their work as possible. Supervisors should be advised on how to identify repetitive jobs with low stimulation and skill utilization and enriching these jobs with extra activities and initiatives, including involvement of more decision authority and more opportunities for skill use and development for employees.

Implications for reducing low work social support are more ‘psychosocial’ than ‘socio-technical’. However, supervisors should be encouraged to provide as much help and support to the employees as required and in good time whenever and if possible.

Supervisors should try to provide clear information on job tasks to their employees, avoiding unclear and confusing instructions.

10.7.2.2. Psychosocial interventions

According to Parkes and Sparkes (1998) psychosocial interventions, in general, involve improvements in perceived autonomy in the workplace, clearer job roles, and improvements in communications and social supports among employees and between employees and supervisors, as a means of reducing exposure to work stressors.

Initiatives could be put in place by organizations for reducing work-related morbidity and enhancing wellbeing among their employees. This can be achieved by: (i) enhancing coping skills for dealing with work stressors and alleviating symptoms of perceived stress; and (ii) improving general wellbeing through health screenings and lifestyle modification.

Organizations could arrange special seminars in the workplace, which employees could attend for free during lunch breaks or after work and which would provide training on efficient ways of dealing with work stressors, such as time management, prioritization of workload and successful coping skills for working under pressure. Seminars on assertiveness skills, anger management, as well relaxation techniques could help employees in alleviating the adverse symptoms of exposure to work stressors. Even though there is evidence that relaxation techniques, such as breathing exercises, meditation or yoga can reduce stressor-induced autonomic activation (Peng et al, 1999; Bernardi et al, 2001), evidence on whether these techniques could reduce risk of disease outcomes is inconclusive (Rees et al, 2004).

For a reduction in high job demands, employees should be encouraged to report any conflicting demands and/or intense working conditions with low availability of time, rather than experiencing these in quite. Of course, this would need reorganization of the whole working environment in order for the employee to feel safe to report such adverse working conditions without risking losing their job. For a reduction in low job control, employees should be encouraged to discuss concerns with their supervisors about limited control in their tasks. This active dialogue could also help release tensions.

10.7.2.3. Empirical findings from worksite interventions

Few studies have investigated the effects of worksite interventions for a reduction in stressors on employee subjective stress and health indicators. A review aiming specifically to examine the evidence on the effectiveness of organizational interventions on reducing work stress concluded that structural interventions with randomised control designs are very rare. The specific review identified only 1 randomised-control intervention study on the effect of structural interventions on physiological outcomes (Parkes & Sparkes, 1998). Another review of the literature looking at evidence on the benefits of interventions for reducing work-related stress, which specifically aimed at comparing organisational interventions with individual interventions, concluded that studies looking at the effect of organizational interventions on disease outcomes were

lacking (van der Kling et al, 2001). The few studies looking at the effectiveness of interventions for reducing exposure to work stressors at the workplace level are described below.

In an intervention study in Sweden involving supervisor training for provision of appropriate esteem and recognition to employees, it was shown that employees who worked under these newly trained supervisors had reduced cortisol secretion (Theorell et al., 2001). In a study among Japanese blue-collar workers, stressor reduction measures resulted in a reduction in depressive symptoms in the intervention compared to the control worksites, which was still evident at the 2-year follow-up, as well as a reduction in the proportion of employees who took sick leave (Kawakami et al, 1997).

Siegrist (2005) suggests that resistance against such changes should be expected from decision makers where the main argument points to the negative cost-benefit relation of respective investments. However, in an economic study that aimed at exploring common organizational features of companies that were most successful in terms of shareholder value, the following characteristics were determined as of the greatest importance: (i) employment security; (ii) selective hiring of new personnel; (iii) self-managed teams and decentralized decision making as the basic principles of organizational design; (iv) comparatively high compensation contingent on organizational performance; (v) extensive training; (vi) reduced status distinctions and barriers across levels; (vii) extensive sharing of financial and performance information throughout the organization (Pfeffer, 1998). Obviously all the above result in high job control and social support among employees, thus in a way this evidence supports the notion that a reduction in psychosocial work stressors would benefit an organization.

10.7.3 Implications at the individual level

If and when what was discussed in sub-sections 10.6.1 and 10.6.2 is put into practice, what remains to be done at the individual level is for people to perceive the importance of their stress experience in relation to physical disease. In other words, exposure to

psychosocial stressors should begin to be interpreted in people's minds as any other harmful exposure, such as smoking, an unhealthy diet, being obese, having high blood pressure and so on.

Prevention at the individual level mainly involves attempts to reduce work-related stress among individuals exposed to psychosocial work stressors. Usually, at the individual level, there is always the argument that in a democratic society people should be left alone to make their own choices for their health and indeed many people disagree with too much of a health-oriented society. However, unlike smoking, high fat/high sugar diets or even obesity, there is nothing enjoyable in being exposed to work stressors. The challenge in this case is not for people to be motivated about avoiding or dealing with such exposures but about finding the way out; finding the way to escape or deal with work-related stress. It is beyond the scope of the current project to discuss how individuals could find different ways to deal with stressful experiences, but the issue will be discussed briefly.

One obvious escape from a stressful work environment would be to seek another job. This falls in the concept of people learning not to underestimate the potential of their stressful experience for causing disease. People would more easily leave from a job in which they are exposed to physical hazards, than from a job where they are exposed to psychosocial hazards. Better perception of the harms in physical health related to exposure to psychosocial stressors would be thus an important starting point. If change of job is not an option then the other way round is effective coping with stress. Even though the most successful coping types have been identified in the literature (i.e. approach copings) (Litman, 2006), it is very difficult to control or change personal tendencies towards coping (Furham & Jaspars, 1983). In fact, individuals are more likely to employ avoidance coping, involving selective ignoring (generally considered an inefficient coping mechanism) in the workplace rather than in other spheres of life (Fleishman, 1984). Prevention at the individual level could also involve attempts to reduce morbidity associated with work-related stress among individuals exposed to psychosocial work stressors.

The main point that should be made about individual level implications is that individuals should not ignore their stressful experience in the workplace but instead try to find the way that best works for them in dealing with their stress. This is a challenge as health providers, such as GPs, cannot provide confident recommendations which are backed by empirical evidence on ways of reducing stressful experiences and their symptoms. The usual recommendation that individuals receive is “try not to stress too much” or “try to avoid stressful situations”, which is hardly helpful for the individual. Empirical evidence is needed therefore on specific lifestyle modifications that could help reduce subjective stress and stress-related disease outcomes in individuals.

Overall, implications at the societal, worksite and individual level lack backing from empirical evidence. Research on interventions aiming at reducing exposure to psychosocial work stressors among employees is still in an infant stage. Therefore, the effects of intervention programmes in reducing subjective stress as well as disease outcomes among employees are largely unknown. Better provision of information through education programmes on the health hazards of exposure to psychosocial work stressors, at all levels, will benefit stress-related public health.

10.7.4 Psychosocial work stressors and implications for health inequalities

Reduction of psychosocial stressors, including work stressors has been amongst the main recommendations of a governmental report on reducing health inequalities in the UK. The Acheson report published in 1998 aimed at investigating the main reasons for the social gradient in health and disease (Acheson, 1998) recognized that no public policy should be enacted without considering the implications for health of all citizens. The report proposed three models for explaining the social gradient in health: (i) the neo-materialist model; (ii) the cultural/behavioural model; and (iii) the psychosocial model. The third model, the psychosocial, theorizes that psychosocial stressors are affecting the lower social classes more than the higher and recognizes the psychosocial work stressors

as among the most important psychosocial stressors that need to be tackled to reduce health inequality in the UK society.

The Health Survey for England has shown that T2DM is socially patterned in the UK society. Prevalence of T2DM is higher among lower SEPs and this is more pronounced among women (Sporston & Primatesta, 2003). Findings from this project point to the direction that psychosocial work stressors may contribute, to a large or smaller extent, to this health inequality among women at least. The role of psychosocial work stressors in explaining social inequalities in T2DM was not the scope of this project, but studies investigating this would be very useful for informing policy initiatives for a reduction in health inequality.

10.8 Overall conclusions

- Psychosocial work stressors, characterised by a combination of high job demands and low job control are associated with an elevated risk of T2DM. This risk is elevated even further in co-occurrence of low social support at the workplace. Failed reciprocity, characterised by an imbalance between efforts and rewards at the workplace, is also associated with an elevated risk of T2DM. These associations are only observed among women and are more pronounced in the lower SEPs and obese individuals. There is a need for more studies looking at gender differences and effect modifications in the effect of psychosocial work stressors on T2DM.
- Among a population of white collar middle-aged healthy Caucasian women, the excess risk associated with exposure to psychosocial work stressors is estimated to be between 2-4 cases per 1000 person-years. Elimination of psychosocial work stressors among this population of women is estimated to prevent 10-15% of all T2DM cases. This a substantial impact in the population but still relatively small compared to the huge impact of the growing obesity epidemic on incident T2DM. Yet, the interaction between work stressors and obesity observed in this project

highlights a potentially important role for psychosocial work stressors in relation to incidence of T2DM in the population.

- Pathophysiological changes linked to exposure to psychosocial work stressors, characterised by increased accumulation of body fat, an adverse lipid profile and low grade inflammation, explain a third of the association between these work stressors and incident T2DM. These risk factors are affected by other environmental exposures as well thus it cannot be said that they are direct biomarkers of exposure to work stressors. Health behaviours do not provide any explanation for the effect of work stressors on T2DM, probably due to the complexity of the overall determinants of health behaviours, as well as the not so accurate assessment of behavioural factors in epidemiological studies. Other potential pathways linking psychosocial stressors to T2DM need to be investigated in order to strengthen the case for causality for this association.
- Experimental studies designed to manipulate the working environment in a way to decrease exposure to work stressors among employees, with monitoring of health effects, could help confirm the importance of exposure to work stressors in public health.
- Reduction of exposure to work stressors in the public could help reduce the burden of T2DM in the UK population. Reduction of exposure to work stressors could also help reduce health inequalities as individuals exposed to work stressors are more likely to come from lower SEPs.

Table 10.1 overleaf summarizes how evidence from this project extends knowledge on the role of psychosocial work stressors on development of T2DM.

Table 10.1 Contribution of current findings in extending the knowledge on the field of psychosocial work stressors and type 2 diabetes

What is already known on this subject?

- Exposure to job strain is associated with higher prevalence of T2DM among women in cross-sectional analyses.

What does this project add?

- Simultaneous exposure to job strain *and* low social support at work (iso-strain) further increases the risk of T2DM among women. Exposure to conditions of high efforts spend and low rewards gained in the workplace is associated with increased risk of T2DM among women.
- The effect of psychosocial work stressors on T2DM is higher among lower SEP and obese individuals.
- 35-44% of T2DM cases among Caucasian middle-aged white-collar women exposed to work stressors is estimated to be attributed to this exposure, while 10-15% of all cases in this population are estimated to result from exposure to work stressors, assuming a causal association.
- Biological factors (obesity, HDL-cholesterol and markers of inflammation) explain 1/3 of the effect of psychosocial work stressors on T2DM, while health behaviours do not provide any substantial mediation in this effect.

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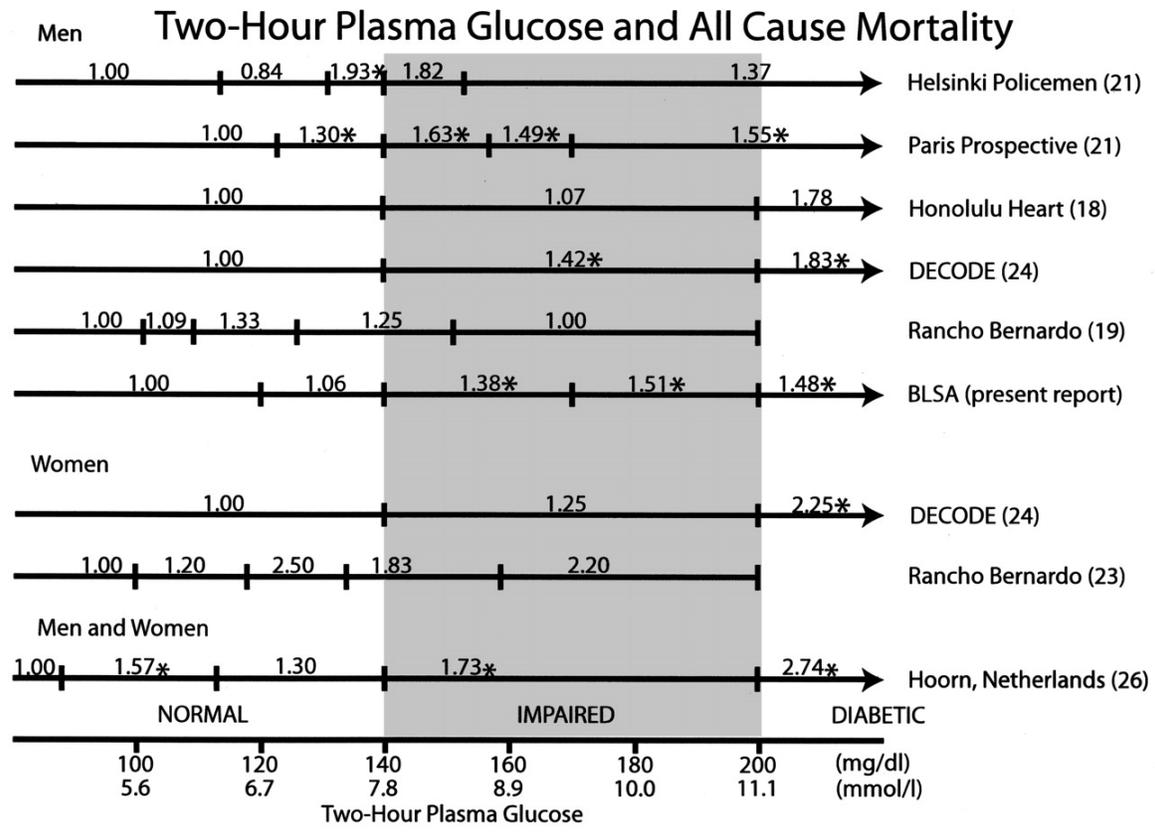
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Appendices

Appendix 1 Blood glucose and Mortality

Table A1 Association between blood glucose levels and all-cause mortality



Appendix 2 Description of project variables

Table A2 Summary table with brief description of the variables used in the current project

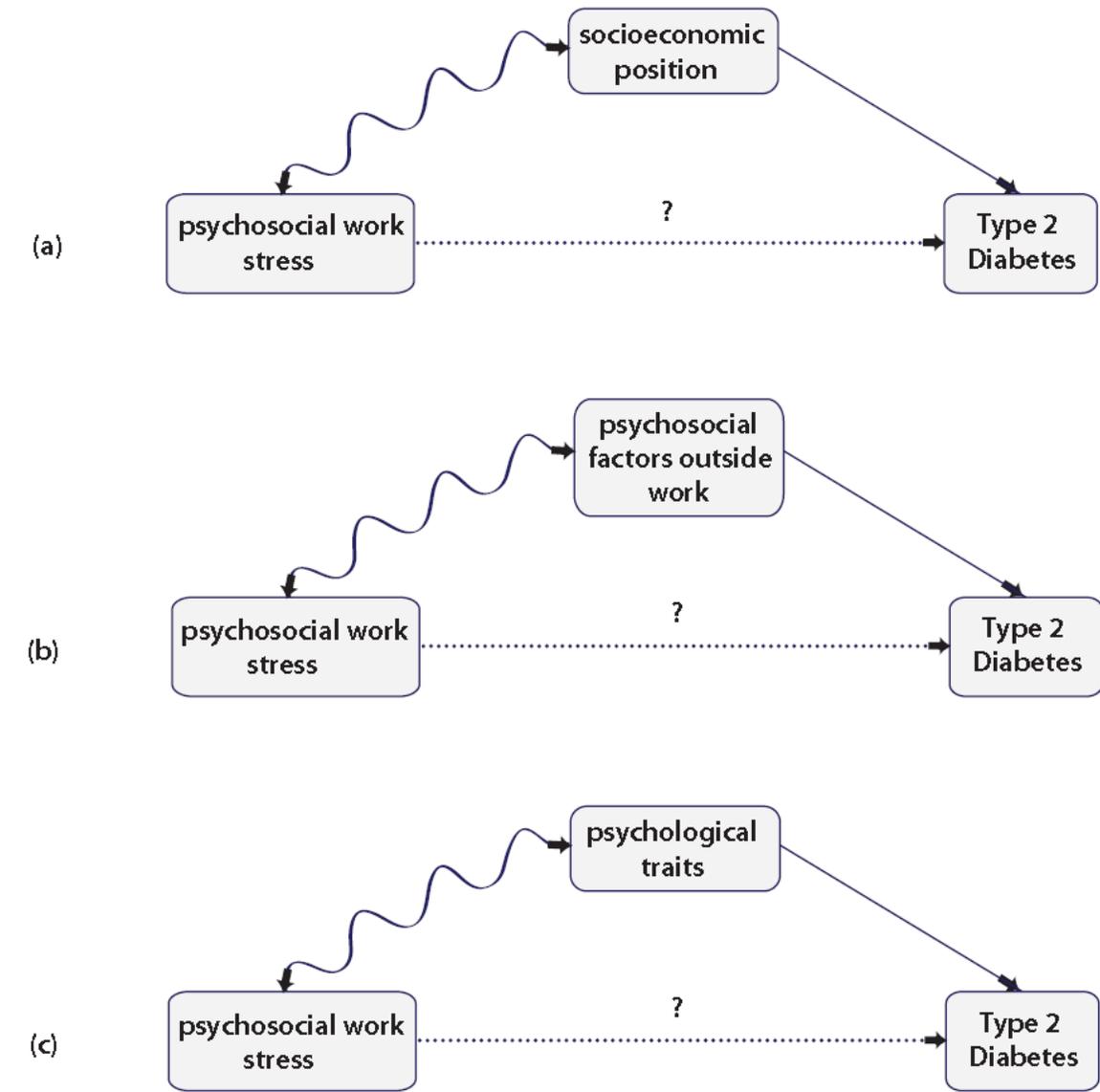
variable	description	units/categories	development	phase	type
<i>type 2 diabetes</i>	oral glucose tolerance test, supplemented by fasting glucose and self-reported doctor-diagnosed diabetes; WHO criteria, 1999	yes / no	ready (already derived for previous analyses)	1-7 and 3-7	binary (time-to-event variable)
<i>psychosocial work stressors</i>					
job strain	Karasek demand/control model of work stress (high demands/low control=job strain)	yes / no	derived (derived for the current project)	3	binary
iso-strain	extension of Karasek demand/control model (high demands/low control/low work social support=iso-strain)	yes / no	derived	3	binary
effort-reward imbalance	Siegrist model of work stress emphasizing the role of failed reciprocity caused by efforts not equaled by rewards	ratio	derived	3	continuous
<i>Socioeconomic</i>					
Employment grade	self-reported Civil Service grade title	administrative / professional / clerical-support	ready	3	ordered categorical
educational attainment	self-reported highest qualification achieved	university degree / secondary education / no formal education	ready	3	ordered categorical
father's social class	self-reported father's main occupation	non-manual (I, II, IIINM) / IIIM / IV+V	ready	1 and 5	ordered categorical
<i>Psychosocial factors outside work and psychological traits</i>					
life satisfaction	self-reported feeling of financial security, satisfaction with standard of living, material deprivation, and general life satisfaction.	score (0-30)	ready	1	continuous

upset by life events	7 items derived from the 'Life Event and Difficulty Schedule' questionnaire	score (0-21)	ready	1	continuous
Isolation	self-reported social networking	score (0-6)	ready	1	continuous
anger	self-reported personality traits (10 items)	score (0-30)	ready	1	continuous
hostility	22-item version of the Cook-Medley hostility scale	score (0-37)	ready	1	continuous
affect balance	10-item Bradburn affect balance scale	score (-15 to 15)	ready	1	continuous
type A personality	The Framingham Type A questionnaire	score (0-30)	ready	1	continuous
chronic general psychological wellbeing	30-item version of the General Health Questionnaire	score (0-30)	ready	1-3	continuous
Behavioural					
alcohol consumption	self-reported consumption of beer, wine and spirits	units per week	ready	3	categorical
smoking status	self-reported smoking or ex smoking	never / ex / current	ready	3	categorical
physical activity	self-reported time spend in mild, moderate and vigorous activities	MET-hours per week	ready	3	continuous
dietary patterns	calculated from a semi-quantitative 127-item food frequency questionnaire (FFQ) using cluster analysis	healthy / Mediterranean-like / sweet / unhealthy	ready	3	categorical
dietary energy density	calculated from FFQ by dividing energy intake from food (kcal) by the mass of all solid food consumed (g)	kcal/g	derived	3	continuous
wholegrain cereal consumption	calculated from FFQ as per week consumption of brown bread, wholegrain bread, shredded wheat, muesli, bran-flakes, porridge, brown rice, wholegrain pasta	grams per day	derived	3	continuous
Energy intake underreporting	Based on the Goldberg cut-off for identifying unrealistically low energy intakes based on physical activity level	yes / no	derived	3	binary
Energy Intake:Total Energy Expenditure	Ratio of energy intake to total energy intake derived for adjusting for diet misreporting	ratio	derived	3	continuous
Anthropometric					

height	measured with a stadiometer with participants in the Frankfort plane	cm	ready	3	continuous
Body Mass Index	measured weight divided by height squared	kg/m ²	ready	3	continuous
waist circumference	measured in the standing position using a tape-measure as the smallest circumference at or below the costal margin	cm	ready	3	continuous
waist-hip ratio	waist circumference divided by hip circumference	ratio	ready	3	continuous
waist-height ratio	waist circumference divided by height	ratio	derived	3	continuous
Cardiometabolic					
systolic blood pressure	measured in the clinic according to a standard protocol	mmHg	ready	3	continuous
triglycerides	measured in the clinic according to a standard protocol	mmol/l	ready	3	continuous
HDL cholesterol	measured in the clinic according to a standard protocol	mmol/l	ready	3	continuous
Inflammatory					
fibrinogen	measured in the clinic according to a standard protocol	g/l	ready	3	continuous
C-reactive protein	measured in the clinic according to a standard protocol	mg/l	ready	3	continuous
Interleukin-6	measured in the clinic according to a standard protocol	ng/l	ready	3	continuous
von Willebrand factor	measured in the clinic according to a standard protocol	IU/ml	ready	3	continuous
factor VII	measured in the clinic according to a standard protocol	IU/ml	ready	3	continuous
Reproductive					
menopausal status	single question on whether periods have stopped	yes / no	ready	3	binary
hormone replacement therapy	single question on whether ever taken hormone replacement therapy	yes / no	ready	3	binary
contraceptive pill use	single question on whether ever taken oral contraceptive medication	yes / no	ready	3	binary

Appendix 3 Confounding and Mediation in the Main Association

Figure A1 Set of illustrations on how different factors could potentially confound the work stress-type 2 diabetes association



Women only

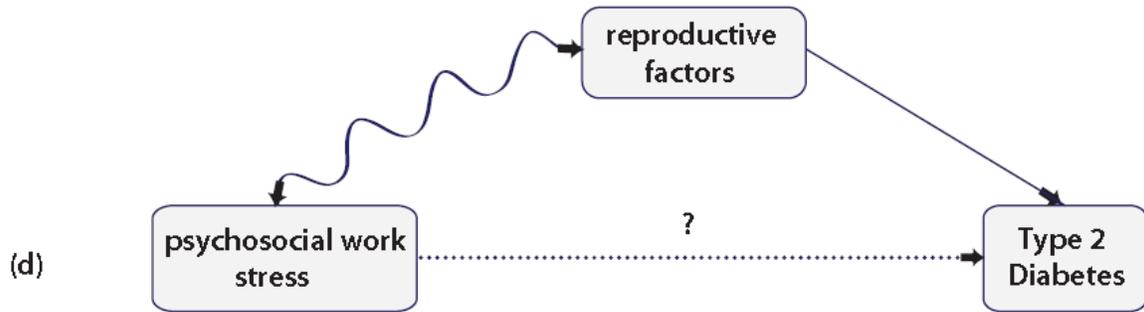
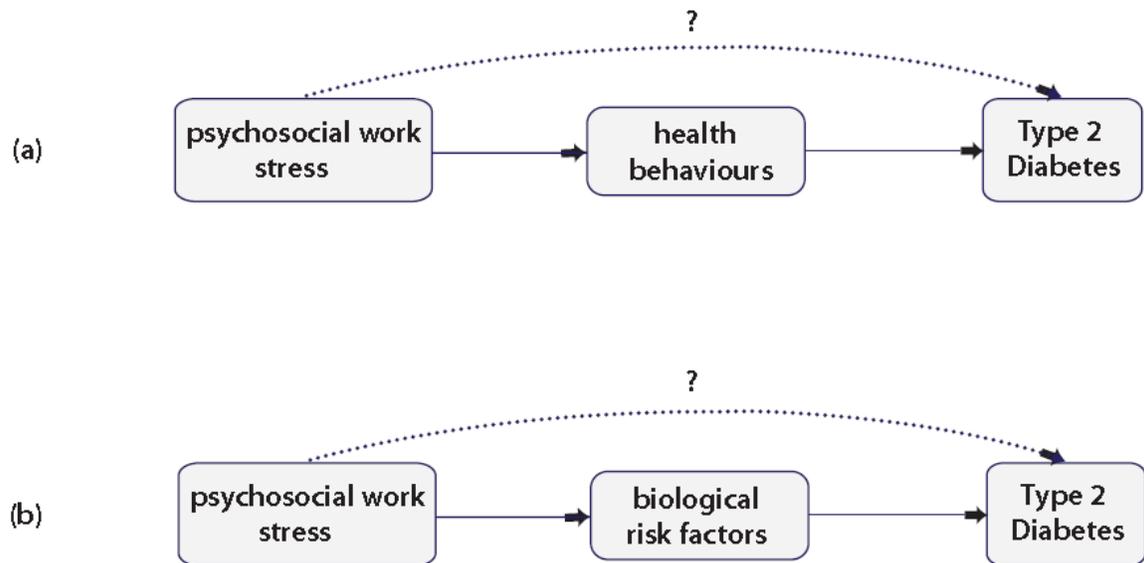


Figure A2 Set of illustrations on how different factors could potentially mediate the work stress-type 2 diabetes association



Appendix 4 Distribution of Main Variables and Other Derived Variables

Figure A3 New type 2 diabetes cases identified during follow-up (1985-2004) among men and women in the WII study

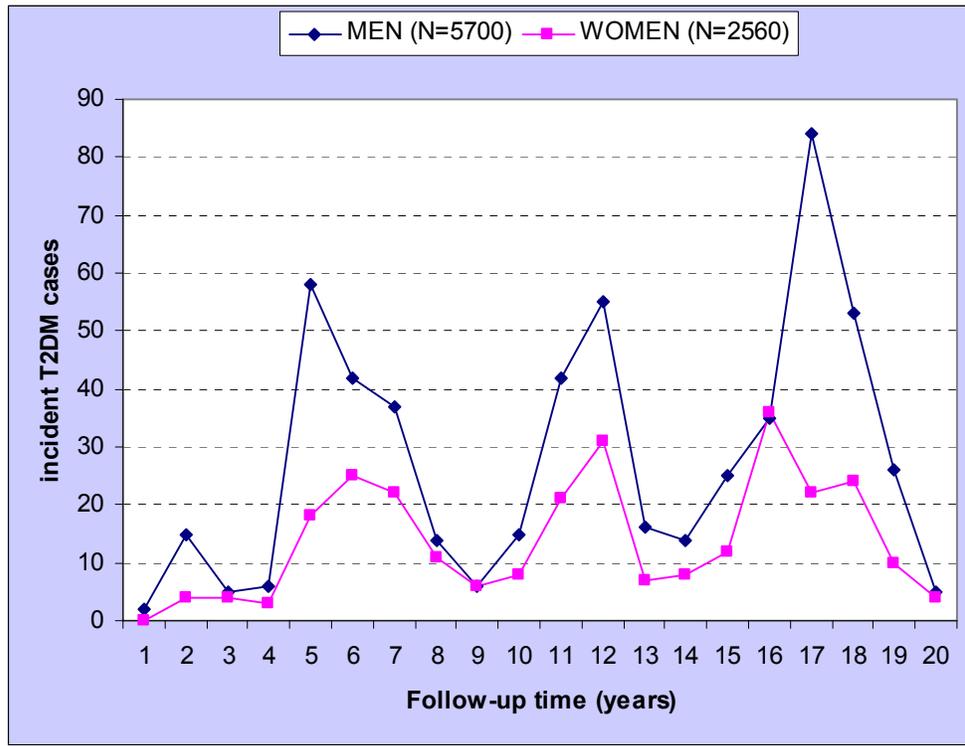


Figure A4 Distribution of job demands (1991-93) among men and women in the WII study

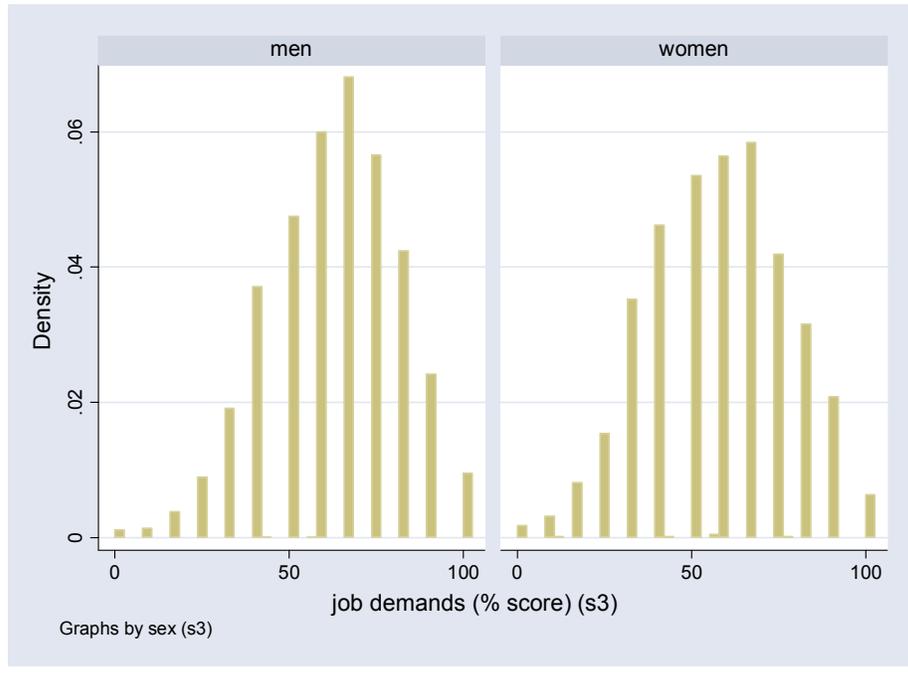


Figure A5 Distribution of job control (1991-93) among men and women in the WII study

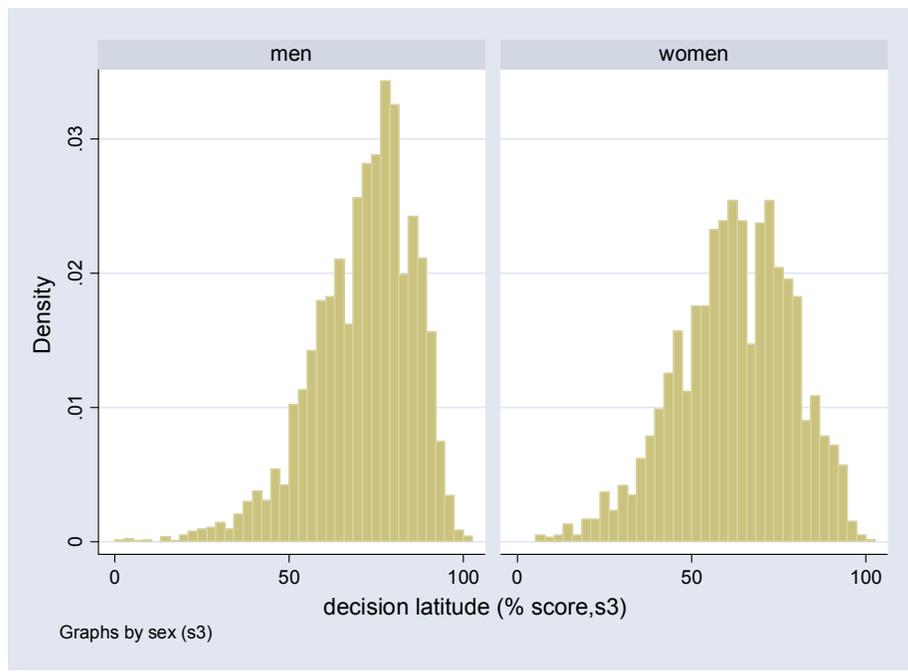


Figure A6 Distribution of social support at work (1991-93) among men and women in the WII study

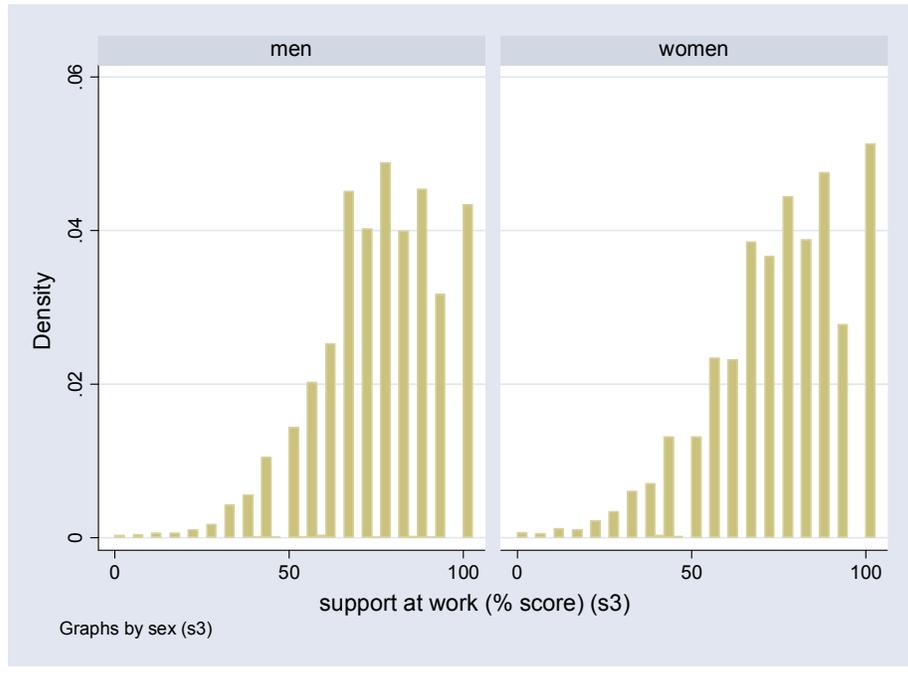


Figure A7 Distribution of efforts at work (1991-93) among men and women in the WII study

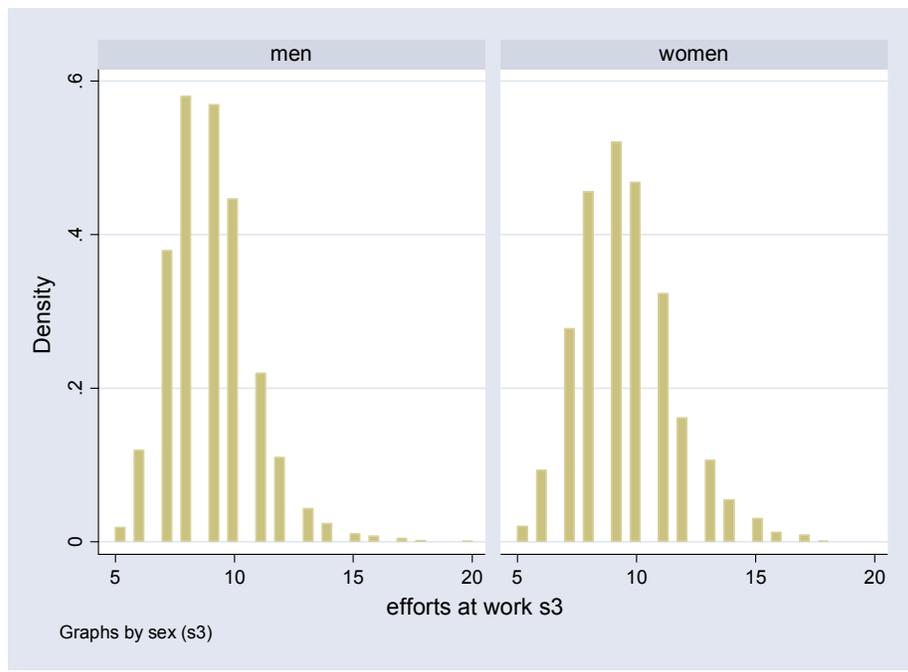


Figure A8 Distribution of rewards at work (1991-93) among men and women in the WII study

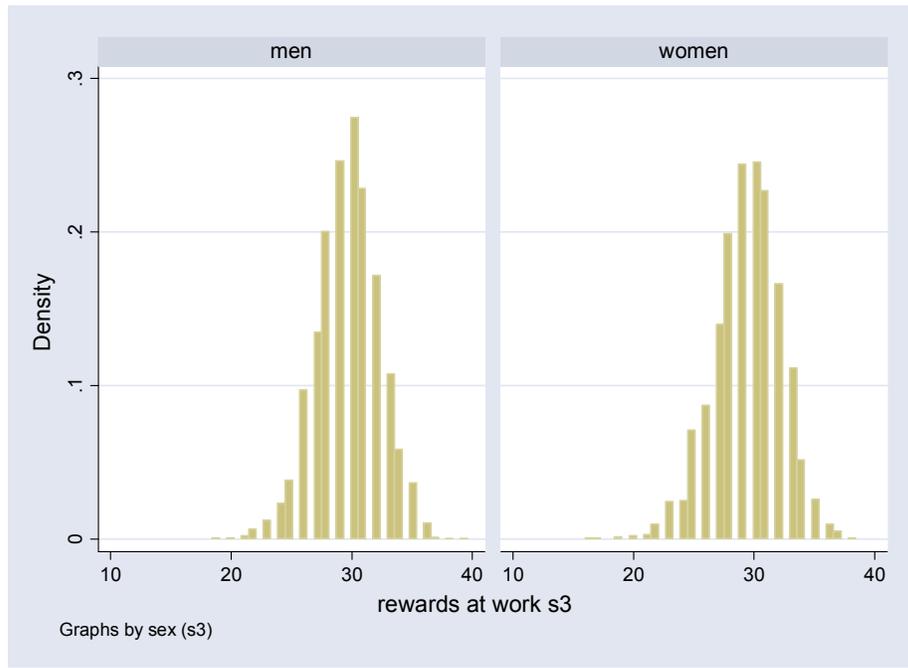


Figure A9 Distribution of effort-reward imbalance (1991-93) among men and women in the WII study

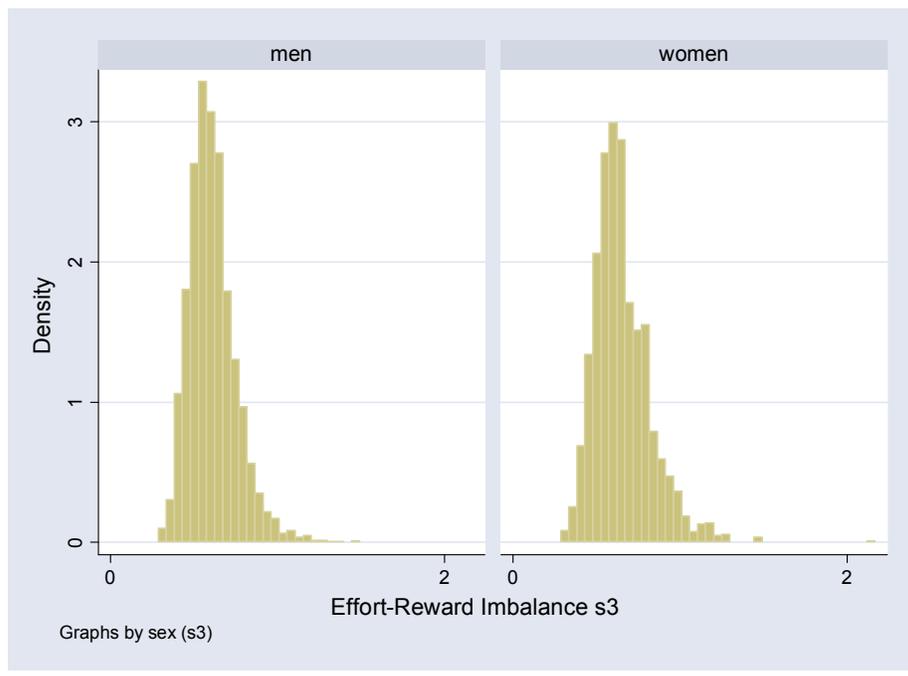


Figure A10 Distribution of dietary energy density (1991-93) among men and women in the WII study

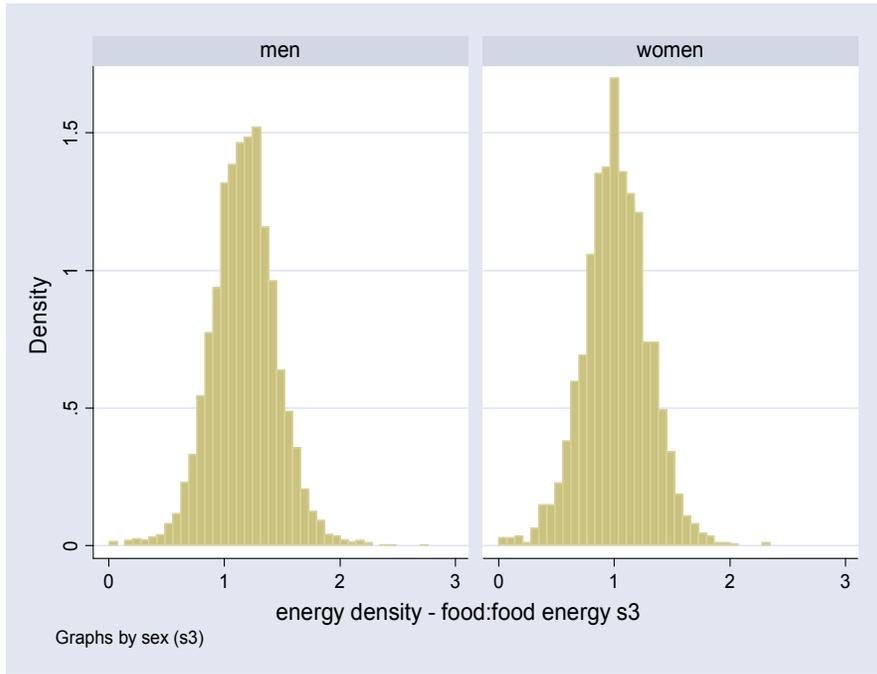


Figure A11 Distribution of wholegrain cereal consumption (1991-93) among men and women in the WII study

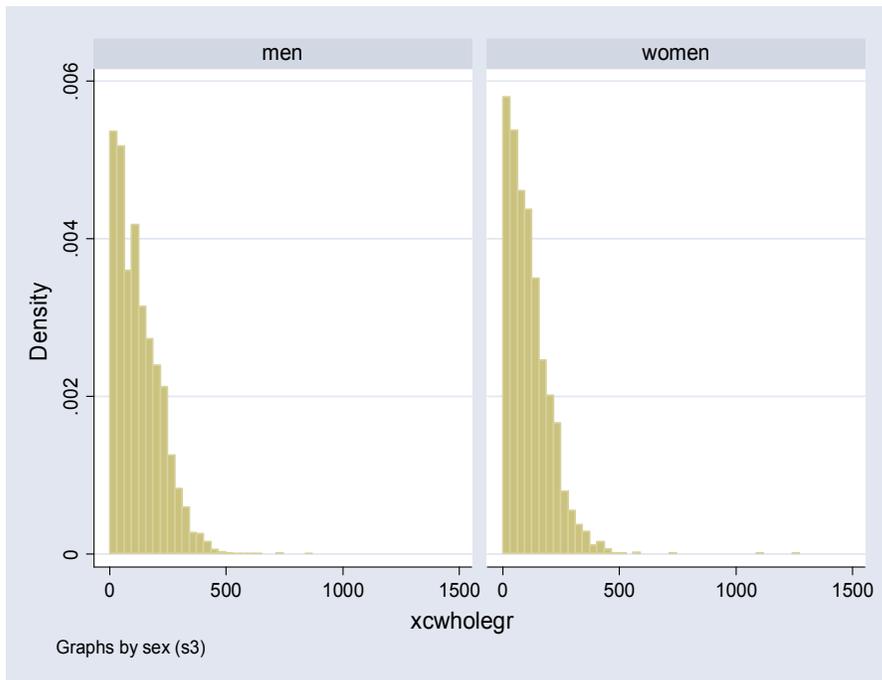


Figure A12 Distribution of Energy Intake:Total Energy Expenditure (1991-93) among men and women in the WHI study

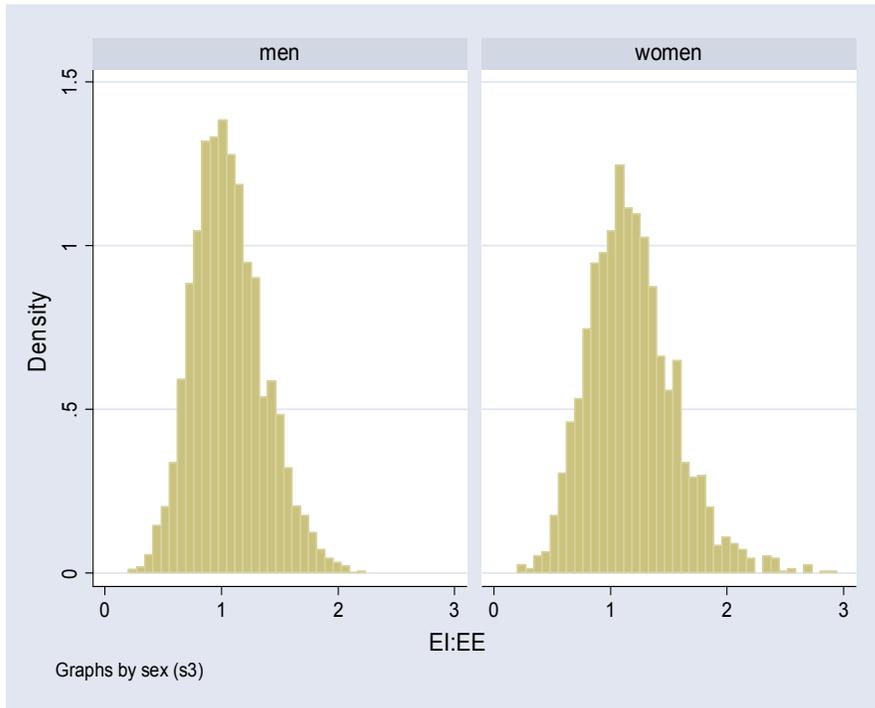
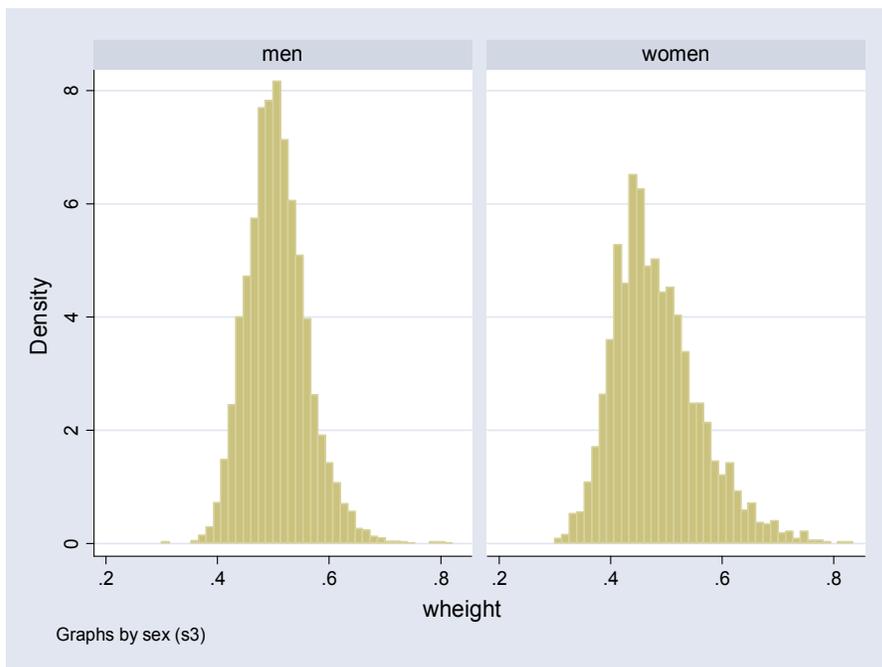


Figure A13 Distribution of waist-height ratio (1991-93) among men and women in the WHI study



Appendix 5 Evidence on Factors Associated with Incident T2DM in WII

Table A2 Summary table showing which socioeconomic, psychosocial, behavioural and biological characteristics were independently associated with T2DM among men and women after 15 years of follow-up in the WII study

	MEN		WOMEN	
	Effect	Strength	Effect	Strength
Potential confounders				
Employment grade	✓	strong	✓	strong
Upset by life events	✓	moderate	✗	n/a
Potential mediators				
Alcohol consumption	✗	n/a	✓	moderate
Smoking status	✓	strong	✗	n/a
Dietary pattern	✓	moderate	✗	n/a
Dietary energy density	✗	n/a	✓	weak
Wholegrain cereal	✓	moderate	✗	n/a
Physical activity	✓	moderate	✓	weak
Height	✓	strong	✓	strong
BMI	✓	strong	✓	strong
Waist circumference	✓	strong	✓	strong
Waist-hip-ratio	✓	strong	✓	strong
Waist-height ratio	✓	strong	✓	strong
Systolic blood pressure	✓	strong	✓	strong
Triglycerides	✓	strong	✓	strong
HDL-cholesterol	✓	strong	✓	strong
Fibrinogen	✓	moderate	✓	moderate
C-reactive protein	✓	moderate	✓	moderate
von Willebrand factor	✓	moderate	✗	n/a

Appendix 6 Iso-strain and Risk Factors Among Men

Table A3 Cross-sectional associations between iso-strain and T2DM risk factors at phase 3 of the WII study among men

	No iso-strain	Iso-strain	<i>p-value for difference</i>
Smoking status (%)			
never	48.8 (1684)	46.8 (217)	
ex	40.5 (1398)	36.2 (168)	
current	10.7 (370)	17.0 (79)	<0.001
Dietary pattern (%)			
healthy	30.1 (963)	29.2 (127)	
Mediterranean-like	19.3 (617)	15.6 (68)	
sweet	17.4 (556)	18.9 (82)	
unhealthy	33.1 (1059)	36.3 (158)	0.21
Wholegrain cereal (mean)	127.5 (1.64)	117.7 (4.30)	0.038
Physical activity (mean)	3.74 (0.05)	3.41 (0.12)	0.013
Unhealthy behaviour score	0.55 (0.01)	0.69 (0.03)	<0.001
BMI (mean)	25.3 (0.05)	25.5 (0.15)	0.11
Waist circumference (mean)	89.7 (0.15)	90.2 (0.45)	0.27
Waist-height ratio (mean)	0.50 (0.001)	0.51 (0.003)	0.072
WHR (mean)	0.92 (0.001)	0.93 (0.003)	0.14
Triglycerides (mean)	1.58 (0.02)	1.67 (0.06)	0.14
HDL (mean)	1.32 (0.01)	1.29 (0.02)	0.18
Systolic blood pressure (mean)	122.0 (0.22)	120.0 (0.57)	0.012
Fibrinogen (mean)	2.33 (0.01)	2.31 (0.03)	0.52
CRP (mean)	1.80 (0.07)	1.44 (0.09)	0.077
IL-6 (mean)	1.80 (0.04)	1.69 (0.07)	0.32
vWf (mean)	106.7 (0.70)	102.8 (2.03)	0.95
Factor VII (mean)	89.9 (0.53)	88.8 (1.17)	0.43
Metabolic syndrome (%)	15.9 (545)	17.7 (83)	0.31

Table A4 Cross-sectional associations between iso-strain and factors associated with incident type 2 diabetes at phase 3 of the WII study among LOW GRADE men

	No iso-strain	Iso-strain	<i>p-value for difference</i>
Smoking status (%)			
never	42.3 (77)	33.3 (10)	
ex	31.3 (57)	30.0 (9)	
current	26.4 (48)	36.7 (11)	0.47
Dietary pattern (%)			
unhealthy+sweet	69.9 (93)	66.7 (14)	0.76
Wholegrain cereal (mean)	114.5 (8.83)	87.8 (15.52)	0.24
Physical activity (mean)	2.72 (0.20)	2.46 (0.44)	0.63
Unhealthy behaviour score	1.13 (0.07)	1.18 (0.14)	0.78
BMI (mean)	25.8 (0.26)	26.0 (0.71)	0.11
Waist circumference (mean)	91.0 (0.77)	92.9 (2.49)	0.27
Waist-height ratio (mean)	0.53 (0.005)	0.54 (0.014)	0.29
WHR (mean)	0.94 (0.005)	0.95 (0.011)	0.58
Triglycerides (mean)	1.70 (0.07)	2.30 (0.39)	0.014
HDL (mean)	1.29 (0.03)	1.31 (0.07)	0.83
Systolic blood pressure (mean)	123.2 (0.98)	121.8 (2.16)	0.58
Fibrinogen (mean)	2.50 (0.05)	2.38 (0.09)	0.29
CRP (mean)	2.03 (0.22)	2.07 (0.40)	0.94
IL-6 (mean)	2.07 (0.13)	2.23 (0.40)	0.64
vWf (mean)	118.2 (3.47)	127.3 (13.48)	0.95
Factor VII (mean)	91.5 (1.88)	92.1 (5.19)	0.43
Metabolic syndrome (%)	23.4 (43)	16.7 (5)	0.87