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**EPIDEMIOLOGICAL
STUDIES ON TYPE 2
DIABETES: ASSESSMENT
OF DIABETES RISK
FACTORS AND STUDY
PARTICIPATION**

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ABSTRACT

Type 2 diabetes is a disease with increasing prevalence. Better knowledge of risk factors may form the bases for specific interventions and preventive measures. The aim of this thesis was to contribute to the knowledge on type 2 diabetes, by examining family history of diabetes and other risk factors with emphasis on psychological exposures.

The studies are based on the cohort of the Stockholm Diabetes Prevention Program (SDPP) in which 12,952 men and 19,416 women 35-56 years old were screened for diabetes and diabetes in close relatives. The baseline health examination comprised 3,128 men and 4,821 women of whom 50% had a family history of diabetes. An oral glucose tolerance test identified 65 men and 63 women with previously undiagnosed diabetes, and 228 men and 208 women with pre-diabetes (IFG, IGT or IFG+IGT). At the follow-up 8-10 years later, 2383 men and 3329 women were re-examined. 183 men and 106 women were then classified with diabetes, and 291 men and 211 women with pre-diabetes. In study IV, diabetes was assessed according to filled prescriptions of anti-diabetic drugs 2005-2008, through record linkage to the Swedish Prescribed Drug Register. The health examinations included body measurements, and information was obtained by questionnaire on life style, psychosocial, personality and socioeconomic factors. Prevalence odds ratios (OR) with 95% confidence intervals (CI) were calculated in logistic regression analyses for cross-sectional and prospective studies.

Our findings indicate that a family history of diabetes is an important risk factor in both men and women. A combined exposure to a family history of diabetes and another risk factor, such as obesity, physical inactivity, smoking or low sense of coherence (capacity to cope with stressors) had a greater effect on type 2 diabetes than any of these factors alone. Biologic interaction was not suggested, with the exception for the combination of a family history of diabetes and obesity in women with pre-diabetes. High psychological distress conferred a two-fold increased risk for type 2 diabetes and pre-diabetes in men, and in women middle scores were associated with an almost two-fold increase of pre-diabetes. Among personality traits, low antagonism in men was associated with a reduced risk of having abnormal glucose regulation (pre-diabetes or type 2 diabetes), as were high hedonic capacity in both men and women. No significant associations were found with the impulsivity, negative affectivity, and alexithymia scales. Non-response bias did not seem to be present at screening- and baseline steps indicating that diabetes prevalence and risk may be estimated from a cohort study such as the SDPP. At follow-up, the overall risk for diabetes was slightly lower in the study group, although the effect of this for the association studies was limited.

In conclusion, a combined exposure to a family history of diabetes and lifestyle factors had greater effect on type 2 diabetes than any of these factors alone. There was no cross-sectional biologic interaction between studied risk factors, except for a family history of diabetes and obesity in women with pre-diabetes. Psychological distress seems to be involved in the aetiology of type 2 diabetes, at least for men. In addition, some personality traits may be associated with abnormal glucose regulation.

Keywords: cohort, family history of diabetes, lifestyle, personality, psychological distress, screening, type 2 diabetes

LIST OF PUBLICATIONS

The thesis is based upon the following papers, which will be referred to by their Roman numerals:

- I. Hilding A, Eriksson A-K, Agardh EE, Grill V, Ahlbom A, Efendic S, Östenson C-G. The impact of family history of diabetes and lifestyle factors on abnormal glucose regulation in middle-aged Swedish men and women. *Diabetologia*. 2006;49:2589-2598.
- II. Eriksson A-K, Ekbom A, Granath F, Hilding A, Efendic S, Östenson C-G. Psychological distress and risk of pre-diabetes and type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabet Med*. 2008;25:834-842.
- III. Eriksson A-K, Gustavsson JP, Hilding A, Granath F, Ekbom A, Östenson C-G. Personality traits and abnormal glucose regulation in middle-aged Swedish men and women. *Diab Res Clin Pract*. 2012;95:145-152.
- IV. Eriksson A-K, Ekbom A, Hilding A, Östenson C-G. The influence of non-response in a population-based cohort study on type 2 diabetes evaluated by the Swedish Prescribed Drug Register. *Eur J Epidemiol*. 2012 (in press).

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
FHD	Family history of diabetes
HP5I	Health-relevant Personality 5-factor inventory
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LADA	Latent autoimmune diabetes in adults
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
OR	Odds ratio
SD	Standard deviation
SDPP	Stockholm Diabetes Prevention Programme
SEP	Socioeconomic position
SI	Synergy index
SOC	Sense of coherence

1 BACKGROUND

1.1 TYPE 2 DIABETES

1.1.1 Definition and description

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia. The chronically elevated blood glucose levels of diabetes in conjunction with other metabolic disturbances, i.e. dyslipidemia, are associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels¹. Diabetes increases the risk for stroke or myocardial infarction four to six times².

The vast majority of diabetes cases fall into two categories: Type 1 diabetes, where the cause is an absolute deficiency of insulin secretion, and type 2 diabetes, where the cause is a combination of insulin resistance which decreases the ability of the liver, skeletal muscle and adipose tissue to respond to insulin, and inadequate compensatory insulin secretion from the β -cells of the pancreas³. Type 2 diabetes often develops insidiously through asymptomatic pre-stages, where a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues may be present long before diabetes is diagnosed. Individuals having a pre-stage of diabetes have a higher risk of developing diabetes¹. Also prior gestational diabetes, i.e. elevated blood glucose levels during pregnancy, increases the risk for later type 2 diabetes³. Type 2 diabetes accounts for 85-95% of all diabetes cases¹. Latent autoimmune diabetes in adults (LADA) is a form of diabetes in between type 1 and type 2 diabetes with a prevalence of approximately 5-10% among adults with non-insulin-requiring diabetes. It is a slowly progressive form of autoimmune or type 1 diabetes with onset in adult age, and that can be treated initially without insulin injections⁴.

1.1.2 Occurrence

The prevalence of type 2 diabetes varies greatly between different parts and populations of the world, ranging from approximately 3-4% in Sub-Saharan Africa⁵ to up to 38-50% among Pima Indians in North America^{6,7}. The prevalence of diabetes in Sweden is still relatively low and has been estimated to about 3-5%^{2,8,9}. Both stable^{10,11} and increased^{12,13} prevalences in Sweden have been reported recently. One component behind increased prevalence is the improved survival of patients¹⁴. It should be noted though, that among non-European immigrants being 60 years of age and living in Stockholm, the prevalence has been estimated to 14.6%, twice the prevalence in the Swedish-born subjects, 6.9%¹⁵.

The number of people with diabetes is increasing globally due to population growth, aging, urbanization and increasing obesity and physical inactivity¹⁶. The most dramatic increase in the prevalence of diabetes is seen in developing and newly developed nations, particularly in the Pacific and Indian Ocean region, and Asia, as a result of industrialization and westernization of lifestyles (including high-energy diets and reduced physical activity). The increased prevalence of diabetes is also seen in disadvantaged communities in developed nations, e.g. native Americans, Afro-

Americans and Mexican Americans in the USA, native Canadians, Australian Aboriginies and Torres Strait islanders, and Polynesians in New Zealand¹⁷. Certain populations have a high propensity for type 2 diabetes implicating a genetic susceptibility which in combination with changed life circumstances results in increasing prevalence of the disease^{6,18}.

The total number of people with diabetes across the world will increase from 285 million in 2010 to 439 million in 2030 in one projection which is based on population aging and urbanisation. The three countries with highest numbers of estimated cases of diabetes for 2010 and 2030 are India, China and U.S., and highest prevalence has Nauru, United Arab Emirates, and Saudi Arabia/Mauritius⁵. Also the increase in obesity is considered epidemic^{18,19}.

Besides that diabetes reduces quality of life for individuals and families, the direct and indirect costs associated with diabetes and diabetes related complications will put a heavy burden on the society^{20,21}.

1.2 RISK FACTORS

Type 2 diabetes is a complex disease of multiple aetiology which has both genetic and environmental components. Type 2 diabetes is regarded to be triggered by environmental factors in genetically susceptible individuals²².

1.2.1 Genetic factors and family history of diabetes

Type 2 diabetes has a clear familial component and this is a result of both shared environmental effects and genes²². The risk is increased in individuals with affected first-degree relatives. A family history of diabetes has been reported to increase the risk 2-4-fold in low-prevalence populations²³⁻²⁵. The details of the genetic influence of type 2 diabetes remain to be fully understood. At this point, more than 36 diabetes-associated genes primarily involving β -cell dysfunction has been identified in genome-wide association studies. However, only around 10% of the heritability can be explained by these genes, each of them having a small influence and representing common variants in multiple gene loci²⁶. The high prevalence of type 2 diabetes in certain populations has sometimes been ascribed to a “thrifty” genotype. This genotype is believed to offer a survival advantage in early societies by favouring fat deposit during periods when food was abundant, to better survive times of famine^{27,28}, however, this has not directly been proved²⁸.

1.2.2 Environmental factors

1.2.2.1 Obesity

Obesity is the most prominent environmental risk factor for developing type 2 diabetes²⁹. However, obesity is, like type 2 diabetes, also influenced by genetics³⁰. The duration of obesity plays a role^{22,31}. It has been shown that different measures of body size; BMI, waist circumference, and waist-to-hip ratio all are associated with type 2 diabetes³². In obese individuals, the adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors

which are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet β -cells, failure to control blood glucose levels follows^{33,34}. It is important to note that not all obese individuals develop type 2 diabetes, and also non-obese individuals develop type 2 diabetes²². Other factors must be involved.

Interaction effects between abdominal obesity and hyperglycemia have been reported where the association between abdominal obesity and hyperglycemia was stronger in the presence of a parental history of diabetes, in addition to that the individuals with a parental history of diabetes were more obese³⁵. Also, biologic interaction between family history of diabetes and obesity has been suggested³⁶. Otherwise, little is known regarding the possible presence of biologic interaction effects between different risk factors influencing the risk of type 2 diabetes. Biologic interaction implies that the joint effect of two risk factors is greater than the sum of the independent effects³⁷. With prevention in focus synergy effects is an important field of study. If biologic interaction is being present between two factors, this would imply that the elimination of one risk factor also reduces the risk of the other³⁸.

1.2.2.2 Health behaviours

Physical inactivity^{39,40} and tobacco use⁴¹⁻⁴² confers an increased risk for type 2 diabetes. Coffee consumption has been associated with decreased risk⁴³ while consumption of alcoholic drinks, depending on reported amounts of intake, can either decrease or increase the risk of developing diabetes⁴⁴.

1.2.2.3 Socioeconomic factors

In western societies, type 2 diabetes is more prevalent in lower socioeconomic groups and materially deprived areas⁴⁵⁻⁴⁷. This can partly be attributed to that certain risk factors are being more prevalent, i.e. obesity, smoking, and sedentary lifestyles^{48,49}. Recently, the incidence of type 2 diabetes was reported to be associated with a low socioeconomic position whether measured by educational level, occupation or income in high-, middle, and low-income countries, although data from middle- and low-income countries were limited⁵⁰. In Sweden, about 20% of the burden of type 2 diabetes can be attributed to low education levels⁵¹. Also, within civil servants a social gradient measured by employment grade has been observed for incident diabetes⁵².

1.2.2.4 Psychosocial stress and depressive symptoms

The notion that mental or emotional stress can contribute to the aetiology of diabetes mellitus can be tracked back at least 300 years. And by the end of the 19th century, William Maudsley, considered by many to be the founder of modern psychiatry, wrote that diabetes is sometimes caused in man by mental anxiety. He had observed that diabetes often followed the occurrence of a sudden trauma⁵³.

Although the literature is not extensive, a variety of concepts related to stress or emotional stress, and sleep problems have been studied in relation to type 2 diabetes. In one study major stressful life events were related to the prevalence of type 2 diabetes, and accumulating of visceral fat did not explain this association⁵⁴. Low decision latitude at work and low sense of coherence has been associated to type 2 diabetes in women⁵⁵. In the same study, high demands at work showed no association with type 2 diabetes. In another study of different psychosocial factors in civil servants⁵² only effort-reward imbalance, in men, was associated with type 2 diabetes. Furthermore,

depressive symptoms or disorder have been prospectively related to type 2 diabetes^{56,57}. Also associations between sleep disturbances and incidence of diabetes have been reported^{58,59}, although not all studies found an association⁶⁰.

In 2006, a meta-analysis was published compiling the results of the nine available prospective studies published between 1996 and 2004 on depression as a risk factor for type 2 diabetes mellitus⁶¹. A somewhat increased risk for type 2 diabetes in depressed individuals was reported, pooled relative risk 1.37 (1.14-1.63). The studies compiled in the meta-analysis used a variety of instruments for measuring depression which may have influenced the results, and the authors pointed to the need for further exploring the influence of depressive symptoms on type 2 diabetes⁶¹.

The biological mechanisms involved in the associations between stress and type 2 diabetes may embrace that stress contributes to hyperglycemia, possibly through activation of the sympathetic nervous system and the HPA-axis. Activation of the HPA-axis causes excessive cortisol production, which may lead to long-term consequences such as insulin resistance, dyslipidaemia, visceral obesity and type 2 diabetes⁶²⁻⁶³. Also immunological processes have been proposed⁶⁴⁻⁶⁶.

1.2.2.5 Personality

Hostility and anger have been associated to blood glucose and insulin levels⁶⁷⁻⁶⁹, abdominal obesity⁷⁰ and type 2 diabetes⁷¹. Also, hostility and anger have been reported to be risk factors for cardiovascular disease^{72,73} which partly share aetiology with type 2 diabetes⁷⁴. Anxiety is suggested to predict⁷³, and negative affect has shown a weak association to coronary heart disease⁷⁵. It may be noted that concepts such as anger/hostility or anxiety may generally be referred to in the literature somewhat differently, such as personality traits, behaviour, emotions or emotional stress. Hostility and anger have been studied in relation to type 2 diabetes to a limited extent, and even less is known about if other personality traits influence the risk of type 2 diabetes. Hypothetically, the same mechanisms as proposed for depression including hormonal arousal in response to stress could be responsible for possible influences on type 2 diabetes risk^{62,63}.

Trait theory is a specific field in personality psychology that deals with individual differences. Personality traits refer to consistent patterns in the way individuals behave, feel and think. There is no single trait theory, however most scientists in this field believe that inherited biological factors are primary determinants of individual differences in traits. The paramount interest of trait researchers is measurement, and a trait taxonomy is an overall descriptive scheme within which any and all persons can be described. A large body of research involving factor analyses indicates that five major factors are necessary and reasonably sufficient for a taxonomy of individual differences. Interestingly, individual words that describe persons in the everyday language, were the starting point from which the five-factor model of personality was developed⁷⁶.

The five major personality factors are called: Neuroticism, that contrasts emotional stability with a broad range of negative feelings, including anxiety, sadness, irritability, and nervous tension. Openness to experience, which describes the breadth, depth, and complexity of an individual's mental and experiential life. Extraversion and agreeableness, that both summarizes the traits that are interpersonal; that is, they capture what people do with each other and to each other. Finally, conscientiousness,

which primarily describes task- and goal-directed behaviour and socially required impulse control⁷⁶. The text in this and the previous paragraph was compiled from information in *Personality: Theory and research*, by Cervone & Pervin, 2008.

2 AIMS

The general aim of this thesis was to contribute to the understanding of the aetiology of type 2 diabetes, by examining family history of diabetes and other risk factors, with emphasis on psychological exposures. In addition, the objective was to consider some methodological aspects relevant for observational studies including diabetes cohort or screening studies.

The specific aims of the individual papers were:

Study I: To investigate the influence of family history of diabetes, body mass index, smoking, physical inactivity, and sense of coherence and to evaluate if family history of diabetes acts in biological synergy with these exposures to influence pre-diabetes or type 2 diabetes.

Study II: To estimate the role of self-reported psychological distress, including symptoms of anxiety, apathy, depression, fatigue and insomnia, as a predictor of pre-diabetes and type 2 diabetes.

Study III: To examine personality traits antagonism, impulsivity, hedonic capacity, negative affectivity and alexithymia in association with abnormal glucose regulation.

Study IV: To evaluate potential selective non-response or non-participation at the screening-, baseline-, and follow-up steps of Stockholm Diabetes Prevention Programme. Also, to analyse if our previous association studies have resulted in false risk estimates for type 2 diabetes associated with different exposures.

3 MATERIAL AND METHODS

3.1 STUDY DESIGN

The studies in the present thesis are based on the population-based cohort of Stockholm Diabetes Prevention Programme (SDPP).

3.1.1 Baseline study

A short questionnaire was sent to all men born 1938-1957 living in Sigtuna, Tyresö, Upplands Bro and Värmdö in Stockholm and all women born 1942-1961 living in the same municipalities and one additional municipality; Upplands Väsby, asking about country of birth and presence of diabetes in subjects and in relatives (Fig. 1). The study population was identified through the Stockholm County Council Register. Answers were obtained from 79% (10236/12952) of men and 85% (16481/19416) of women. Individuals were excluded due to diabetes (2.5% men and 1.5% women), foreign origin (2.1% men and 7.6% women), family history of diabetes (FHD) that was unclear (27.4% men and 28.5% women) and insufficient FHD (15.0% men and 9.9% women). A restriction in the female sample had to be done due to financial reasons which excluded 35- to 44-year-old subjects born in the last third of each month.

At a second step, subjects with FHD together with subjects randomly selected among those without FHD, matched to the first group by age and municipality, were invited to a health examination. In total, 3162 (69.8%) men and 4946 (70.3%) women accepted the invitation. FHD was self-reported by the subjects and defined as known diabetes in at least one first degree relative (parent or sibling) or at least two second-degree relatives (grandparents, uncles or aunts), with diabetes onset generally at the age above 35 years (less than 6% were below 35 years). The sample was enriched to 50% with subjects having a family history of diabetes (FHD).

The participants underwent a standardised oral glucose tolerance test (OGTT), body measurements and answered an extensive questionnaire about smoking habits, physical activity, diet, socioeconomic and psychosocial factors. Uncertain heredity, incomplete examinations and (for women) pregnancy, breast-feeding and medical reasons excluded 34 men and 125 women. Thus, the final baseline study group comprised 3128 men and 4821 women.

3.1.2 Follow-up study

After 8-10 years, the baseline study sample was again invited to a health examination. Subjects diagnosed with type 2 diabetes at baseline, 65 men (2.1%) and 63 women (1.3%), were excluded together with subjects who had moved outside Stockholm County, 239 men (7.6%) and 333 women (6.9%). In total 78 men (2.5%) and 60 women (1.2%) had died during the follow-up period. Of the remaining 2746 men and 4365 women who received an invitation, 2385 men (86.9%) and 3336 women (76.4%) went through a health examination the same as on the baseline occasion. Participants diagnosed with diabetes during the follow-up period did not undergo the OGTT. A

fasting blood sample was taken and also information on year of diagnosis and type of treatment.

In total, 361 men (13.1%) and 1029 women (23.6%) did not wish to participate or could not be reached. After the examinations two men and seven women were excluded due to reporting type 1 diabetes, not answering the questionnaire or because efforts to take a blood sample had failed. The total follow-up study group then comprised 2383 men and 3329 women, representing 76.2% and 69.1% respectively, of the baseline study population.

All subjects gave informed consent and the study was approved by the ethics committee of Karolinska University Hospital.

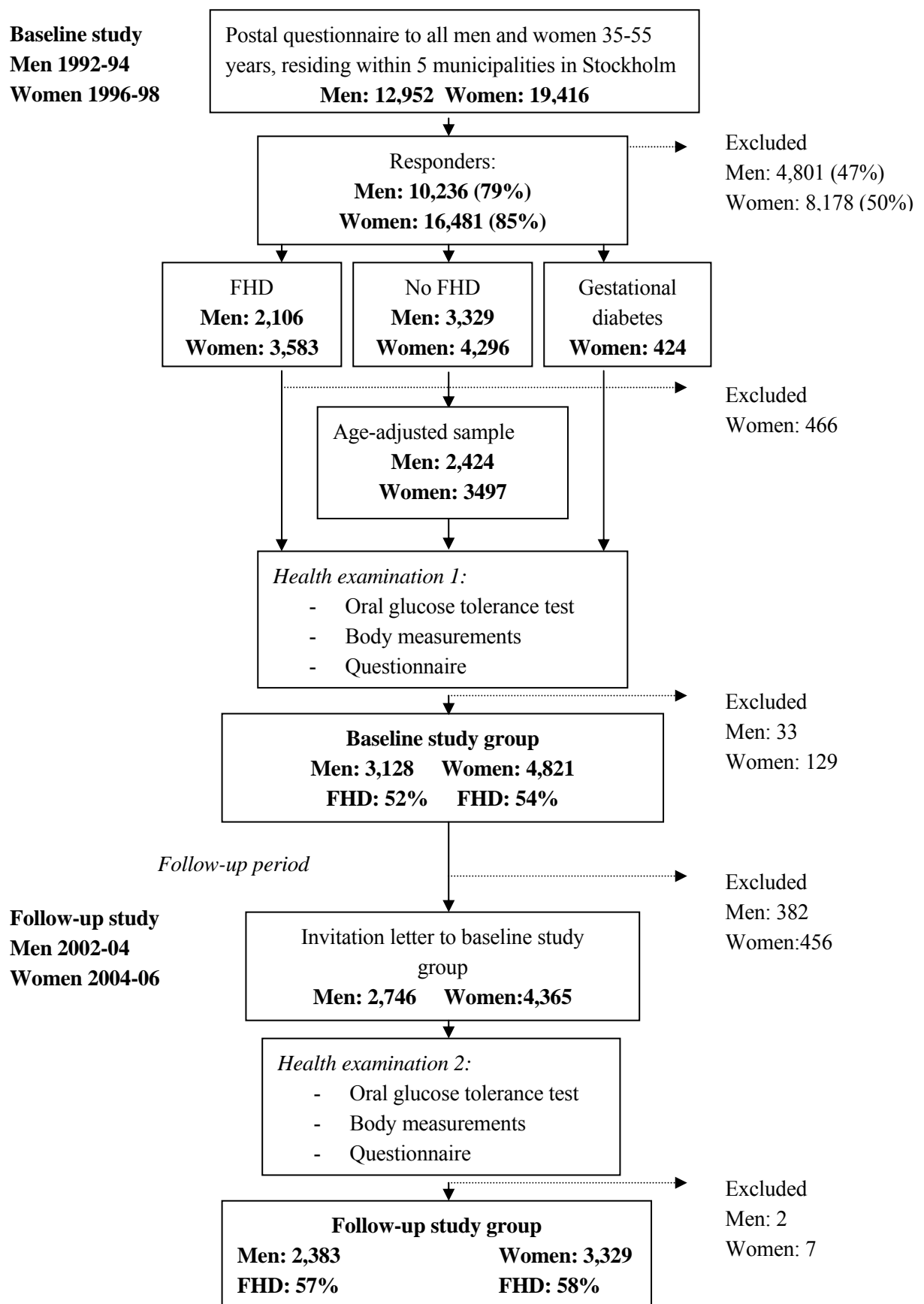


Figure 1 Study design of Stockholm Diabetes Prevention Programme

3.2 CLASSIFICATION OF GLUCOSE TOLERANCE

Classification of glucose tolerance according to the OGTT followed the WHO criteria from 1998⁷⁷. An individual was classified as having normal glucose tolerance (NGT), when the fasting plasma glucose level was <6.1 mmol/l and the 2-h plasma glucose level was <7.8 mmol/l. Impaired fasting glucose (IFG) referred to a fasting plasma glucose value of 6.1-6.9 mmol/l, and a 2-hour value of <7.8 mmol/l. Impaired glucose tolerance (IGT) corresponded to a fasting plasma glucose level of <6.1 mmol/l and a 2-h value of 7.8-11.0 mmol/l. Impaired fasting glucose+impaired glucose tolerance (IFG+IGT) referred to a fasting plasma glucose value of 6.1-6.9 mmol/l and a 2-h value of 7.8-11.0 mmol/l. Type 2 diabetes was classified when the fasting plasma glucose value was ≥ 7.0 mmol/l and/or the 2-h plasma glucose value was ≥ 11.1 mmol/l. IFG, IGT and IFG+IGT are referred to as “pre-diabetes”. Also, pre-diabetes+type 2 diabetes are referred to as “abnormal glucose regulation”. In the analyses, the subjects with normal glucose tolerance were treated as the reference group.

3.3 CLASSIFICATION OF DRUG-TREATED DIABETES

Drug-treated diabetes was defined as having filled at least one prescription of anti-diabetic drugs including insulin (ATC code A10 with subgroups) during the time period between July 1, 2005 and November 30, 2008, registered in the Swedish Prescribed Drug Register at the National Board of Health and Welfare. The individuals that had not filled any prescription of anti-diabetic drugs were treated as the reference group.

3.4 MEASUREMENT OF EXPOSURES AND POTENTIAL CONFOUNDERS

3.4.1 Body measurements and health behaviours

Weight and height was registered with the subjects wearing light indoor clothes and no shoes. Waist and hip circumferences were measured with the subject lying down. Body mass index was calculated and categorised as <25.0 (normal weight), 25.0-29.9 (overweight) and ≥ 30 (obesity) kg/m². In paper 1 BMI was dichotomised in two ways: <25.0 vs ≥ 25.0 , i.e. normal weight vs overweight (including obesity); and <30.0 vs ≥ 30.0 , i.e. non-obesity vs obesity.

3.4.1.1 Physical activity

Physical activity was assessed with the question “How physically active have you been during your leisure time during the last year?” The four response options corresponded to: 1) sedentary leisure time, 2) moderate activity, 3) moderate regular activity, and 4) regular exercise and training. In the analyses the answering alternatives were categorized as low, moderate or regular physical activity according to answering alternatives 1, 2 and 3 + 4, respectively. In paper 1, the answers were dichotomised to either physically inactive according to response alternative 1 or physically active according to alternative 2-4.

3.4.1.2 Smoking

Smoking status was based on information in the questionnaire on current and former smoking habits. Subjects were classified in three groups: never, former and current users. In paper I subjects were classified in two groups: current users or non-current users (including never and former users).

3.4.2 Socioeconomic position

Socio-economic position (SEP) was based on self-reported occupational titles and classified according to the standard system elaborated by Statistics Sweden⁷⁸. Analyses were performed in four groups, high (high- and medium-level nonmanual employees), middle (low-level nonmanual employees) low (unskilled and skilled manual workers) and self-employed/farmers.

3.4.3 Psychosocial measures

3.4.3.1 Sense of coherence

Sense of coherence (SOC) is an instrument measuring the ability to cope with life stressors. The theory and instrument was developed by Antonovsky⁷⁹. The original instrument is based on 29 items on the three dimensions comprehensibility, meaningfulness and manageability⁷⁹. Our analysis of SOC is based on three questions according to a simplified method of measurement suggested to capture the essence of the three dimensions and being adequately valid⁸⁰. The three response alternatives gave one, two or three points, and a summed index of the three items was created. SOC was categorised as low (low) or high (lower middle, upper middle, high) according to the distribution of responses among all respondents.

3.4.3.2 Psychological distress

Psychological distress was measured by an index composed of five items in the questionnaire. The question “How often during the latest twelve months have you been troubled by the following symptoms?” was posed for: 1) insomnia; 2) apathy; 3) anxiety; 4) depression; and 5) fatigue; respectively. The answering alternatives were four: 1) ‘never’; 2) ‘occasionally’; 3) ‘sometimes’; and 4) ‘frequently’; and points were given ranging from 1 to 4. All five questions were then summed to an index, maximum score 20. The index was divided into quartiles according to scoring frequencies, men and women combined. In analyses the two median quartiles were combined to one middle group, and the lowest scoring quartile was considered unexposed to psychological distress. “Low” was equivalent to 5-7.5 points, “middle” to 8-12 points, and “high” to 12.5-20 points. The Cronbach’s alpha (reliability of the index) was calculated to 0.80 for men and 0.81 for women. In addition, the single items of insomnia, apathy, anxiety, depression and fatigue were analysed separately. The response alternatives were then divided into three groups: ‘never’ (unexposed, low), ‘occasionally’ and ‘sometimes’ (middle) and ‘frequently’ (high).

3.4.4 Personality

Personality traits were measured with the Hp5i (Health-relevant Personality 5-factor inventory), an instrument intended for large public health surveys and epidemiological studies⁸¹.

The Hp5i describes five narrowly defined personality sub-traits; antagonism, impulsivity, hedonic capacity, negative affectivity and alexithymia. These are facets of the Five Factor Model personality factors; agreeableness, conscientiousness, extraversion, neuroticism and openness, respectively, and are thought to constitute aspects that are relevant for health, within those factors.

Table 1 Item content for the five personality scales

Question/item	No ^a
Antagonism (<i>as a facet of agreeableness</i>)	
I'm good at making sarcastic comments	3
If someone treats you badly, I basically feel you should treat them the same way back	8
If someone criticises me, I'm not afraid of giving sharp and sarcastic answers	13
Anyone who offends me or my family or friends can expect trouble	18
Impulsivity (<i>as a facet of conscientiousness</i>)	
I have a tendency to act on the spur of the moment without really thinking ahead	4
I often take on things too hastily	9
I usually talk before I think	14
I consider myself an impulsive person	19
Hedonic capacity (<i>as a facet of extraversion</i>)	
My life is full of interesting things	1
I find it easy to enjoy life	5
I often feel happy and sort of elated when I'm about to meet a close friend	11
I try to devote my time to things that make me feel involved	16
Negative affectivity (<i>as a facet of neuroticism</i>)	
I often feel uneasy and uncomfortable for no apparent reason	2
I'm easily pressured when told to speed up my work	7
I often get so tense it wears me out	12
An unexpected noise make me jump	17
Alexithymia (<i>as a facet of openness</i>)	
I don't usually analyse my feelings	6
I think people often tend to exaggerate the importance of their emotions	10
I often find it hard to understand what people mean when they talk about their feelings	15
I prefer not to get involved in other people's problems	20

^aOrder of the question/item in the questionnaire

The antagonism scale intends to capture to what extent an individual is being oppositional, sarcastic and argumentative (Table 1). The impulsivity scale estimates a person's tendency to choose rapidly with little thought, act on the spur of the moment and not make plans. The hedonic capacity scale measures someone's ability to enjoy life, be enthusiastic and engage in goal-directed behaviour. The scale of negative affectivity estimates to what extent a person is prone to be nervous, tensed and stressed. The alexithymia scale is supposed to capture individuals who tend to devalue feelings and show a lack of interest in understanding and talking about emotions. The HP5i has been tested with satisfactory results for internal consistency and dimensionality⁸¹ and measurement invariance across sex and different age groups⁸².

Each subscale had a four-point Likert response format including the answering alternatives "does not apply at all", "does not apply very well", "applies pretty much" and "applies completely". The five subscale means for all participants were calculated and categorized into "low", constituting participants that had scored values <1 standard deviation (SD) of the mean of that particular subscale, "middle" ± 1 SD, and "high" >1 SD. This is in line with subscales being approximately normally distributed, and that scores around the mean are considered "normal" according to construction of the scales and theory in personality research. Categorization was made separately in men and women, following the gender specific mean distributions. In the logistic regression models the middle group was used as the reference group and considered unexposed to either high or low values of that particular personality trait.

3.5 DATA ANALYSIS

The basic aim of the data analysis was to compare the prevalence of type 2 diabetes and pre-diabetes in exposed and unexposed subjects. We calculated prevalence odd ratios (OR), that may be interpreted as prevalence rate ratios since the prevalence of the outcome can be regarded as low. The ORs were estimated with 95% confidence intervals (CI) in multiple logistic regression analysis using SAS (SAS Institute, Cary, NC, USA). To take into account potential confounding we used two models, one adjusted for age, and one adjusted for potential confounders such as family history of diabetes, body mass index, smoking, physical activity, socio-economic position, and psychological distress. In study I, testing for potential confounding was made by including BMI, physical inactivity, and current smoking one by one in the logistic regression model. They were retained in the final model if they contributed at least a 10% change in the age-adjusted crude estimate. In study I, biologic interaction between two risk factors was evaluated from the adjusted ORs, and analysed by testing whether the joint effect was greater than the sum of the independent effects of the single factors, i.e. departure from additivity^{37,38}, by calculating the synergy index (SI)⁸³. The SI is defined as equal to $[OR_{11}-OR_{00}] / [(OR_{01}-OR_{00})+(OR_{10}-OR_{00})]$, where the first index digit indicates the absence or presence of FHD and the second index digit indicates the other risk factor. Subjects not exposed to a family history of diabetes or the other risk factor served as the reference group: $(OR_{00})=1$. CIs (95%) for the SI were calculated according to the method of Hosmer and Lemeshow (1992). Comparison of continuous variables and categorical variables between two independent groups was assessed with the unpaired t-test and the χ^2 test, respectively.

4 RESULTS

4.1 STUDY I: FAMILY HISTORY OF DIABETES AND LIFESTYLE

In this cross-sectional study on baseline data, a family history of diabetes was associated with an increased risk of having abnormal glucose regulation. For pre-diabetes the ORs were 1.6 (1.2-2.1) in men, and in women 1.5 (1.1-2.1), when controlled for age, BMI and physical activity (table 2). The corresponding estimates for type 2 diabetes were 3.1 (1.7-5.6) in men and 1.7 (1.0-3.0) in women. In order to evaluate if a family history of diabetes had a different influence on abnormal glucose regulation in men and women a synergy index assessing biological interaction between a family history of diabetes and sex was calculated. When using women without a family history of diabetes as the reference group, men with a family history of diabetes had higher ORs for all groups of abnormal glucose regulation, than women with a family history of diabetes, and men without a family history of diabetes. The synergy index indicated biological interaction between a family history of diabetes and sex, i.e. that the effects of a family history of diabetes and sex were not independent.

Next, we estimated the combined effects of a family history of diabetes and obesity, physical inactivity, smoking, and low sense of coherence, respectively, and estimated synergy indexes.

Obesity and family history of diabetes

Men and women with both obesity and a family history of diabetes, had 6- and 11-fold elevated ORs for pre-diabetes and type 2 diabetes, respectively, compared to non-obese subjects without a family history of diabetes. The synergy index indicated independent effects of obesity and family history of diabetes in men, while in women a synergistic effect was demonstrated for pre-diabetes, SI 2.2 (1.0-4.5) and for pre-diabetes+type 2 diabetes, SI 1.8 (1.0-3.2). Like in men, no biologic interaction was observed between obesity and a family history of diabetes for type 2 diabetes, SI 1.2 (0.5-2.8). Using waist circumference as a measure of abdominal obesity gave similar results.

Physical activity and family history of diabetes

Men that were exposed to both physical inactivity and a family history of diabetes, had an OR of 9.5 (4.1-22.1) for type 2 diabetes as compared to physically active men without a family history of diabetes. For men with pre-diabetes or women with pre-diabetes or type 2 diabetes, the double exposure to physical inactivity and a family history of diabetes did not yield obviously higher ORs than being separately exposed to either of the factors. The synergy indexes suggested that physical inactivity and a family history of diabetes had independent effects.

Smoking and family history of diabetes

The combination of current smoking and a family history of diabetes resulted in an OR for type 2 diabetes of 4.4 (2.0-10.0) in men, while men with pre-diabetes and women with pre-diabetes or type 2 diabetes having both these risk factors had lower or comparable ORs to those exposed for only one factor. SI illustrated no departure from additivity.

Sense of coherence and family history of diabetes

The combined exposure to low SOC and a family history of diabetes gave an approximately two-fold increase of ORs for pre-diabetes in men and women, and for type 2 diabetes in women, compared to the unexposed for both risk factors. In men, a four-fold increase was found for type 2 diabetes for those exposed to both risk factors individuals. However, no synergistic effects were indicated.

Table 2 Odds ratios (OR) for pre-diabetes, type 2 diabetes and the combined group of pre-diabetes plus type 2 diabetes associated with a family history of diabetes in men and women separately and in combinations of family history and sex

	NGT	Pre-diabetes				Type 2 diabetes				Pre-diabetes + Type 2 diabetes			
	<i>n</i>	<i>n</i>	OR	95% CI	SI (95% CI)	<i>n</i>	OR	95% CI	SI (95% CI)	<i>n</i>	OR	95% CI	SI (95% CI)
Men													
Without FHD	1,409	80	1.0			14	1.0			94	1.0		
With FHD	1,415	148	1.6	1.2-2.1		51	3.1	1.7-5.6		199	1.8	1.4-2.4	
Women													
Without FHD	2,144	67	1.0			18	1.0			85	1.0		
With FHD	2,388	139	1.5	1.1-2.1		44	1.7	1.0-3.0		183	1.6	1.2-2.0	
Combinations of men/women and FHD													
Women without FHD	2,144	67	1.0			18	1.0			85	1.0		
Men without FHD	1,409	80	1.8	1.3-2.5		14	1.4	0.7-2.8		94	1.7	1.2-2.3	
Women with FHD	2,388	139	1.5	1.1-2.0		44	1.7	1.0-3.0		183	1.6	1.2-2.0	
Men with FHD	1,415	148	2.9	2.1-3.9	1.4 (0.9-2.4)	51	4.1	2.3-7.1	2.8 (0.9-9.0)	199	3.1	2.4-4.1	1.7 (1.0-2.8)

Prediabetes is IFG, IGT, and IFG+IGT

Biological synergy was analysed with the synergy index (SI)

All analyses are adjusted for age (35-42, 43-50, 51-56), BMI (<25.0, 25.0-29.9, ≥30.0) and physical activity (sedentary, moderately active, regular exercise)

4.2 STUDY II: PSYCHOLOGICAL DISTRESS

In this prospective study, a larger proportion of women (28,5%) had a high baseline psychological distress score, compared with men (13.0%). Men in the highest quartile of psychological distress were more than twice as likely to develop type 2 diabetes as men scoring in the lowest group, when adjusted for age, BMI, FHD, smoking physical activity and SEP (Table 3). Correspondingly, the risk for pre-diabetes was twice as high for high scorers as for low scorers of psychological distress among men. In women, no increased risk of type 2 diabetes associated with psychological distress was found. However, psychological distress was associated with pre-diabetes in the middle-scoring group in women, OR 1.8 (1.1-3.0) compared to the low-scoring group when adjusted for all named potential confounders.

When analysing the five questions separately, each of them yielded about equal ORs. In men, the ORs for fatigue, insomnia, anxiety and apathy in association with pre-diabetes plus type 2 diabetes (combined group to obtain better power) ranged from 1.8 to 2.8 when adjusted for all potential confounders, for the group reporting frequent problems (highest group). For depression, only the association for the middle scoring group in men was significant, OR 1.3 (1.0-1.7) when fully adjusted. In women, none of the single items was associated to abnormal glucose regulation.

4.3 STUDY III: PERSONALITY

In this cross-sectional study on follow-up data, men with low scores on the antagonism scale had a 70% reduced risk of having abnormal glucose regulation, compared to men with middle scores: age-adjusted OR 0.3 (CI 0.2-0.6) which was not altered when also BMI, FHD, smoking, physical activity, SEP and psychological distress were included in the model (table 4). In women, low antagonism was not associated with abnormal glucose regulation. High scores on the antagonism scale were not associated with abnormal glucose regulation in neither men nor women. Analyses of the hedonic capacity scale showed a 50 and 40% decreased risk of having abnormal glucose regulation for men and women, respectively: age-adjusted ORs 0.5 (0.3-0.9) and 0.6 (0.4-1.0), which were unchanged after control for all the potential confounders. For the group reporting low values on hedonic capacity there were no associations in men, although in women an increased risk was observed, age-adjusted OR 1.7 (1.1-2.6) that was no longer significant when adjusted for all the potential confounders, OR 1.4 (0.9-2.4). However, the association for hedonic capacity in women indicated a dose-response pattern. Alexithymia, impulsivity and negative affectivity were not associated with abnormal glucose regulation in either men or women, although high negative affectivity conferred an age-adjusted OR of 1.3 (1.0-1.8) in men, which became non-significant when the potential confounders were entered in the model, OR 1.3 (0.9-1.8). Likewise, for low impulsivity in men, the age-adjusted OR was 0.7 (0.4-1.0), which became non-significant when multi-adjusted, OR 0.7 (0.5-1.1).

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for the association between baseline psychological distress and pre-diabetes and type 2 diabetes at follow-up

Index of psychological distress	NGT	Pre-diabetes ^a			Type 2 diabetes ^a			Pre-diabetes+ type 2 diabetes ^a		Pre-diabetes ^b		Type 2 diabetes ^b		Pre-diabetes+ type 2 diabetes ^b	
	<i>n</i>	<i>n</i>	OR	95% CI	<i>n</i>	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men															
Low	626	75	1.0		26	1.0		1.0		1.0		1.0		1.0	
Middle	951	121	1.1	(0.8–1.5)	51	1.3	(0.8–2.2)	1.2	(0.9–1.5)	1.1	(0.8–1.4)	1.2	(0.7–2.0)	1.1	(0.8–1.4)
High	202	49	2.1	(1.4–3.1)	26	3.3	(1.8–5.7)	2.4	(1.7–3.4)	1.9	(1.2–2.8)	2.2	(1.2–4.1)	2.0	(1.4–2.8)
Women															
Low	431	18	1.0		12	1.0		1.0		1.0		1.0		1.0	
Middle	1612	113	1.7	(1.0–2.8)	29	0.7	(0.3–1.3)	1.3	(0.8–1.9)	1.8	(1.1–3.0)	0.7	(0.3–1.4)	1.4	(0.9–2.1)
High	823	46	1.3	(0.8–2.3)	16	0.7	(0.3–1.5)	1.1	(0.7–1.7)	1.2	(0.7–2.1)	0.5	(0.2–1.2)	0.9	(0.6–1.5)

^a Data adjusted for age (35–42, 43–49 and 50–56 years)

^b Data adjusted for age (35–42, 43–49 and 50–56 years), body mass index (≤ 24.9 , 25–29.9 and ≥ 30.0 kg/m²), family history of diabetes (no/yes), smoking (never, former and current), physical activity (regular, moderate and sedentary) and socio-economic position (high, middle, low and self-employed). Psychological distress score groups represent quartiles, men and women combined, where the middle group refers to the two median quartiles (those between the lower and upper quartiles).

Table 4 Odds ratios (OR) and 95% confidence intervals (CI) for the association between personality traits and pre-diabetes + type 2 diabetes in 2152 men and 3143 women in Stockholm Diabetes Prevention Programme

	Men						Women					
	NGT		Prediabetes+T2D ^a		Prediabetes+T2D ^b		NGT		Prediabetes+T2D ^a		Prediabetes+T2D ^b	
	<i>n</i>	<i>n</i>	OR	(95% CI)	OR	(95% CI)	<i>n</i>	<i>n</i>	OR	(95% CI)	OR	(95% CI)
Antagonism												
Low	166	10	0.3	(0.2-0.6)	0.3	(0.2-0.6)	289	23	1.1	(0.7-1.7)	1.2	(0.7-1.9)
Middle	1349	254	1.0	REF	1.0	REF	2225	158	1.0	REF	1.0	REF
High	321	52	0.9	(0.6-1.2)	0.8	(0.6-1.1)	416	32	1.1	(0.7-1.6)	1.0	(0.6-1.5)
Impulsivity												
Low	266	32	0.7	(0.4-1.0)	0.7	(0.5-1.1)	393	36	1.3	(0.9-1.9)	1.4	(0.9-2.0)
Middle	1353	243	1.0	REF	1.0	REF	2194	152	1.0	REF	1.0	REF
High	217	41	1.0	(0.7-1.5)	0.8	(0.6-1.2)	343	25	1.1	(0.7-1.7)	1.0	(0.6-1.6)
Hedonic capacity												
Low	185	33	1.0	(0.7-1.5)	0.8	(0.5-1.3)	200	24	1.7	(1.1-2.6)	1.4	(0.9-2.4)
Middle	1475	266	1.0	REF	1.0	REF	2236	169	1.0	REF	1.0	REF
High	176	17	0.5	(0.3-0.9)	0.5	(0.3-0.9)	494	20	0.6	(0.4-1.0)	0.6	(0.4-1.0)
Negative affectivity												
Low	141	19	0.8	(0.5-1.3)	0.8	(0.5-1.4)	365	25	0.9	(0.6-1.4)	0.9	(0.6-1.5)
Middle	1448	242	1.0	REF	1.0	REF	2115	155	1.0	REF	1.0	REF
High	247	55	1.3	(1.0-1.8)	1.3	(0.9-1.8)	450	33	1.0	(0.7-1.4)	0.8	(0.5-1.2)
Alexithymia												
Low	187	26	0.8	(0.5-1.2)	0.9	(0.6-1.4)	479	28	0.9	(0.6-1.3)	1.0	(0.6-1.5)
Middle	1435	251	1.0	REF	1.0	REF	2262	166	1.0	REF	1.0	REF
High	214	39	1.0	(0.7-1.4)	0.9	(0.6-1.4)	189	19	1.3	(0.8-2.1)	1.1	(0.7-2.0)

^a Data adjusted for age (43-50, 51-55, 56-60 and 61-66 years)

^b Data adjusted for age (43-50, 51-55, 56-60 and 61-66 years), body mass index (≤ 24.9 , 25.0–29.9 and ≥ 30.0 kg/m²) family history of diabetes (no, yes, insufficient), smoking (never, former and current), physical activity (regular, moderate and sedentary), SEP (high, middle, low and self-employed/farmers) and psychological distress (low, middle and high). Personality traits score groups represent distribution of means for each trait: <1 SD (low) \pm 1 SD (middle) and >1 SD (high).

The middle group is treated as the reference group for all subscales (OR 1.0)

Analyses include participants with information on all potential confounders

4.4 STUDY IV: INFLUENCE OF NON-RESPONSE

In this prospective study, the absolute risks of drug-treated diabetes were similar in responders and non-responders to the initial screening questionnaire, 8.7 and 7.7% in men, and 4.0 and 3.8% in women (table 5). At the baseline step, the absolute risks in participants and non-participants were 8.5 and 7.2% respectively, in men, and 3.8 and 3.2% in women (table 6). The relative comparisons did reveal no increased risks for drug-treated diabetes for non-responders/non-participants compared to responders/participants at neither the screening- nor the baseline step. At the follow-up step, the absolute risks for participants and non-participants were 4.4 and 6.2% respectively, in men, and 1.6 and 2.6% in women (table 7). The relative measures illustrated increased risks for drug-treated diabetes in follow-up non-participants compared to participants.

The proportion of non-responders/non-participants at the screening and baseline steps that later was classified with drug-treated diabetes was about the same in men and women. However, at follow-up, this proportion was higher among women than among men: 39.8% (33/83) of women with drug-treated diabetes and 25.2% (32/127) of men, did not attend the SDPP follow-up.

Subsequently, baseline exposures were studied in association with either type 2 diabetes measured at the SDPP follow-up, or drug-treated diabetes, the results illustrated that previous estimates for FHD, smoking, physical activity, SEP and psychological distress measured in the SDPP did not seem to be overestimated. However, in women, selective non-participation in the SDPP follow-up study was indicated for BMI, whilst the OR for drug-treated diabetes in the obese group ($\text{BMI} \geq 30$) was lower in non-participants, age-adjusted OR 2.8 (1.2-6.9) than in participants OR 13.7 (6.2-30.1). The pattern for men was the opposite, the OR for drug-treated diabetes in obese men was somewhat higher in non-participants, age-adjusted OR 12.0 (3.6-39.3) than among participants OR 10.7 (5.6-20.3), although these estimates were not statistically different from each other.

In addition, the prospective analyses in the present study confirmed the results from study I in that family history of diabetes is an important risk factor in both men and women. Regarding psychological distress the register data mirrored the results from study II, in that women did not have an increased risk for drug-treated diabetes in neither the middle nor high psychological distress groups, and for men as the risk was increased for high psychological distress. The elevated risk for pre-diabetes in men and women reported in study II, was not possible to evaluate with the Swedish Prescribed Drug Register

Table 5 Absolute risks (%) and ORs for drug-treated diabetes in responders and non-responders to the postal screening questionnaire (Step 1). Absolute risks are stratified in age-groups

Filled at least one prescription of anti-diabetic drugs during the period between July 1, 2005 and November 30, 2008												
Men (age)	48-51		52-59		60-67		All		OR ^a	(95% CI)	OR ^b	(95% CI)
	(n=2,045)		(n=4,931)		(n=5,021)		(n=11,997)					
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)				
Responders	73	(4.8)	304	(8.0)	448	(10.7)	825	(8.7)	1.0		1.0	
Non-responders	20	(3.8)	79	(7.1)	92	(11.1)	191	(7.7)	0.9	(0.8-1.1)	0.9	(0.7-1.1)
All	93	(4.6)	383	(7.8)	540	(10.8)	1,016	(8.5)				
Women (age)	44-51		52-59		60-63		All		OR ^a	(95% CI)	OR ^b	(95% CI)
	(n=7,208)		(n=7,287)		(n=3,991)		(n=18,486)					
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)				
Responders	140	(2.4)	270	(4.3)	212	(6.0)	622	(4.0)	1.0		1.0	
Non-responders	32	(2.3)	48	(4.6)	28	(6.7)	108	(3.8)	1.1	(0.9-1.3)	1.0	(0.8-1.2)
All	172	(2.4)	318	(4.4)	240	(6.0)	730	(3.9)				

^aORs adjusted for attained age 2005 (start of the Swedish Prescribed Drug Register) (44-51, 52-59 and 60-67)

^bORs adjusted for attained age 2005 (44-51, 52-59 and 60-67) and socioeconomic position (high, middle, low and self-employed)

Table 6 Absolute risks (%) and ORs for drug-treated diabetes in baseline participants and non-participants (among 11,125 individuals who were invited to the SDPP baseline study) (Step 2). Absolute risks are stratified for information on FHD or gestational diabetes in the postal screening questionnaire

Filled at least one prescription of anti-diabetic drugs during the period between July 1, 2005 and November 30, 2008												
Men	FHD+ (n=1,945)		FHD- (n=2,264)		All (n=4,209)		OR ^a	(95% CI)	OR ^b	(95% CI)		
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)						
Baseline participants	186	(12.2)	66	(4.6)	252	(8.5)	1.0		1.0			
Baseline non-participants	49	(11.6)	40	(4.9)	89	(7.2)	0.9	(0.7-1.1)	1.0	(0.8-1.3)		
All	235	(12.1)	106	(4.7)	341	(8.1)						
Women	FHD+ (n=3,082)		FHD- (n=3,433)		Gestational diabetes (n=401)		All (n=6,916)		OR ^a	(95% CI)	OR ^b	(95% CI)
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)				
Baseline participants	120	(5.0)	40	(1.9)	17	(9.1)	177	(3.8)	1.0		1.0	
Baseline non-participants	35	(5.0)	23	(1.8)	14	(6.5)	72	(3.2)	0.9	(0.7-1.2)	1.0	(0.7-1.3)
All	155	(5.0)	63	(1.8)	31	(7.7)	249	(3.6)				

^aORs adjusted for age attained age 2005 (start of the Swedish Prescribed Drug Register) (44-51, 52-59 and 60-67)

^bORs adjusted for attained age 2005 (44-51, 52-59 and 60-67), family history of diabetes (no/yes), and socioeconomic position (high, middle, low and self-employed)

Table 7 Absolute risks (%) and ORs for drug-treated diabetes in follow-up participants and non-participants, among 7,136 baseline participants classified with normal glucose tolerance (Step 3). Absolute risks are stratified for baseline FHD

Filled at least one prescription of anti-diabetic drugs during the period between July 1, 2005 and November 30, 2008										
Men	FHD+ n=1,356		FHD- n=1,346		All n=2,702		OR ^a	(95% CI)	OR ^b	(95% CI)
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)				
Follow-up participants	76	(6.8)	19	(1.8)	95	(4.4)	1.0		1.0	
Follow-up non-participants	20	(8.2)	12	(4.4)	32	(6.2)	1.4	(1.0-2.2)	1.4	(0.9-2.3)
All	96	(7.1)	31	(2.3)	127	(4.7)				
Women	FHD+ n=2,093		FHD- n=2,341		All n=4,434		OR ^a	(95% CI)	OR ^b	(95% CI)
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)				
Follow-up participants	41	(2.5)	9	(0.6)	50	(1.6)	1.0		1.0	
Follow-up non-participants	24	(3.6)	9	(1.5)	33	(2.6)	1.8	(1.1-2.8)	1.5	(0.9-2.4)
All	65	(2.8)	18	(0.9)	83	(1.9)				

^aORs adjusted for age at baseline (35-42, 43-49 and 50-56)

^bORs adjusted for age at baseline (35-42, 43-49 and 50-56), family history of diabetes (no/yes), body mass index (≤ 24.9 , 25.0-29.9 and ≥ 30.0), smoking (never, former and current), physical activity (regular, moderate and sedentary), socio-economic position (high, middle, low and self-employed) and psychological distress (low, middle and high).

5 DISCUSSION

5.1 THE FINDINGS

5.1.1 Family history and lifestyle

Family history of diabetes was associated with abnormal glucose regulation in men and in women. Biological synergy between a family history of diabetes and sex was demonstrated, and indicated that a family history of diabetes might have a greater influence on the association to type 2 diabetes in men compared to women. The familial component is well known in the aetiology of type 2 diabetes and is important for both men and women^{22-24,84-86}.

The question may be raised if the observation in the present study of a different influence of family history of diabetes in men and women, could be due to misclassification of family history of diabetes. There might be a difference in men and women with regard to knowledge about diabetes in relatives. For example, there could be under-reporting in men, so that among men who claimed they did not have a family history of diabetes there were men that actually had a family history of diabetes. Even if this was not the case in women, and they instead had knowledge of all relatives with diabetes, there is no reason to believe that among men or women, those with disease (cases) and those without (the controls) differed with regard to knowledge about diabetes in their family. The participants did not know if they were going to be classified with abnormal glucose regulation or not. An overestimation in for instance men would appear only if male cases did have a better knowledge about relatives with diabetes compared with male controls. In this context it may be mentioned that the original prevalence of a family history of diabetes at the SDPP screening phase was fairly similar in men and in women, approximately 21.6% in men and 24.5% in women. The slightly higher occurrence in women might be attributed to that the studied women were somewhat older compared to men, and thereby had more relatives with diabetes, or that women may have more knowledge about diabetes in their family.

When the combined effects of a family history of diabetes and other risk factors; BMI, waist, physical activity, smoking and sense of coherence, respectively, were studied, an exposure to two risk factors conferred higher ORs than being exposed to only one risk factor (with one or two exceptions). However, analysis of biologic interaction according to the synergy index indicated no departure from additivity, i.e. no further effect due to the combination of two risk factors, except for the joint effect of a family history of diabetes and obesity in women having pre-diabetes. In men, no synergistic effect between a family history of diabetes and obesity was demonstrated, either for pre-diabetes or type 2 diabetes separately, or for the combined outcome. Thus, it is possible that the interaction between a family history of diabetes and obesity varies between men and women as well as through the progression of milder forms of abnormal glucose regulation to manifest diabetes.

Biologic interaction between a family history of diabetes and obesity has been reported in women with self-reported type 2 diabetes in a large cohort of 32,662 women aged 40-70 years³⁶. Also, interaction (calculated with a product term in a

linear regression analysis) has been reported in relation to fasting plasma glucose³⁵. In the latter study, interaction was found only in women when BMI was used as the measure of body fatness, whereas, in contrast to our study, an interaction in both men and women was found when waist circumference was used. In a study published in 2010 of 2,081 adults 18-79 years old, biologic interaction between a family history of diabetes and overweight/obesity measured with the synergy index was demonstrated in both men and women with self-reported diabetes⁸⁷.

It is important to note that, like type 2 diabetes, obesity has both genetic and lifestyle-related components^{22,30,84} and aggregates in families⁸⁸. However, a recent study reported that BMI and type 2 diabetes may actually share only little genetic variance⁸⁹. Our study can not separate the effects of genetic and lifestyle-related exposures being a part of a family history of diabetes. Family history of diabetes most likely reflects, in addition to the genetic influence also family-shared conditions, such as socioeconomic group, family values, educational levels and eating habits⁹⁰.

The published paper did not include the crude estimates, i.e. adjusted for only age. These results were similar to the results from the published adjusted analysis. However, as expected most point estimates became slightly higher when BMI and physical activity were excluded from the model. For instance, in both men and women, the association between FHD and abnormal glucose regulation became stronger. Additional biological synergy between risk factors was not observed in the crude models.

5.1.2 Psychological distress

Self-reported psychological distress, including symptoms of anxiety, apathy, depression, fatigue and insomnia was associated with later development of pre-diabetes and type 2 diabetes in Swedish middle-aged men. In women, associations between psychological distress and onset of type 2 diabetes was not present, although an association was observed for pre-diabetes. These results are in line with previous longitudinal studies demonstrating an influence of depression on the development of type 2 diabetes^{61,91}. Since our study was published, the body of literature on the issue has somewhat expanded. Studies may include also data on antidepressant use which has been suggested to be involved in the association between depression and type 2 diabetes. However, when anti-depressant drugs are adjusted for, the association between depression and type 2 diabetes seems to persist^{92,93}. Another study on 161,808 postmenopausal women found slightly increased independent risks of incident diabetes with elevated depressive symptoms or antidepressant use⁹⁴. The observed association of antidepressant use and type 2 diabetes has been suggested to be due to confounding by indication (the true association may not exist between the medication and the outcome, but between the indication for the outcome, i.e. depression, and the outcome⁹⁵). Nevertheless, the relation between depression and diabetes is probably complex, and potentially bidirectional, i.e. type 2 diabetes may also lead to depression⁹⁶⁻⁹⁷.

Another issue is the possible role of sleep disturbances in the prospective relation between depression and type 2 diabetes. Sleep problems and depression are related to each other, and also to cardiometabolic diseases (cardiovascular disease, diabetes, and the metabolic syndrome)⁹⁸. Consequently, an association between

depression and cardiometabolic diseases could partly be due to effects of different types of sleep problems. There are insufficient data to conclude whether depression and sleep problems have independent effects on cardiometabolic outcomes according to a recent review⁹⁸. In a Swedish study of 2,663 subjects 45-65 years old, the age-adjusted RR of depression associated with type 2 diabetes in men disappeared after control for other confounders, including difficulties initiating sleep, and difficulties maintaining sleep⁵⁸. In our study, when evaluating the psychological distress index, insomnia was included among the other symptoms.

Our results indicated an increased risk for type 2 diabetes associated with psychological distress in men, however in women only for pre-diabetes. Associations between depression and type 2 diabetes have been reported in studies including only women^{99,100}. Another study in 37,291 subjects in Norway¹⁰¹, demonstrated an association between anxiety and depression and type 2 diabetes for both men and women. Also, lack of associations has been reported for both men and women^{52,58}. Some studies that demonstrated an association between depressive symptoms and type 2 diabetes did not separate the analyses for men and women^{56,102,103}. The type of measurement of depression and diabetes status did vary across the studies, which also applies to the reported meta-analyses.

In this study, we referred to our exposure as symptoms of psychological distress since it was not a validated instrument for diagnosing clinical depression. An instrument diagnosing a narrow span of clinical depression may result in a lower prevalence of depression than questionnaires evaluating self-reported symptoms of depression or distress. An important point is that mental ill-health in the population is hard to define and there is no perfect method for this¹⁰⁴. One meta-analysis evaluating depression as a risk factor for cardiovascular disease resulted in stronger effects for clinical depression, RR 2.69 (1.63-4.43) compared to depressive mood, RR 1.49 (1.16-1.92)¹⁰⁵. Nevertheless, a single simple question about feelings of nervousness, uneasiness, and anxiety may strongly predict suicide attempts and psychiatric disease 5-10 years later¹⁰⁶.

Also when the symptoms were analysed as single entities in association with abnormal glucose regulation (pre-diabetes+type 2 diabetes), symptoms of insomnia, apathy, anxiety and fatigue to a similar extent influenced the risk in men. However, the association in women disappeared. This may be due to that the outcome groups had been combined to one, and also, that the exposure group categories ("low", "middle" and "high") were different when analysing the questions as single entities (compared to the index). It may be mentioned again that the scale of measurement had flaws, including that the two middle answering alternatives looked fairly alike. However, these two answering options were combined to one (i.e. "middle") in the analyses of the single questions. Also, even though the exposure was somewhat misclassified, it should not differ between those with pre-diabetes or type 2 diabetes, and those with normal glucose tolerance since these (cases and controls) were unaware of their disease status at baseline when the exposure was measured.

In our study women reported symptoms of psychological distress to a greater extent than the men did. In recent studies in Sweden it has been documented that women over time self-report more anxiety¹⁰⁷, mental ill-health (GHQ12)¹⁰⁸ and sleeping problems or persistent fatigue¹⁰⁴ than men do, and also use both more in- and out-patient mental health care¹⁰⁷. It is reasonable to assume that the difference in

symptoms reporting between men and women in our study represents an actual difference in psychological distress, but it could also reflect for instance that the content of the questions have a different meaning for men and women, or, a difference in for instance what may be expected from gender roles to report¹⁰⁹. Another possibility is that men and women use different coping strategies to handle psychological distress and that this influences the risk for type 2 diabetes¹⁰⁹. It could be speculated that men under-report feelings of distress, and when they finally admit them they have become severe, and are affecting the neuroendocrine stress systems. Consequently, we could speculate that the influence of psychological distress on type 2 diabetes was diluted in women in our study. On the other hand, an association was noted in women for pre-diabetes in the middle index group. It is possible that the results for women would be different if psychological distress/depression was measured with other instruments⁹⁹⁻¹⁰¹.

5.1.3 Personality

In this cross-sectional study, a reduced risk of previously unknown pre-diabetes or type 2 diabetes was observed for men with low scores on the antagonism scale. This is indirect in accordance with a few previous studies reporting an association between hostility or anger and blood glucose and insulin levels⁶⁷⁻⁶⁹. Also, one prospective study of 11,615 middle-aged men and women has reported a slight overrisk for type 2 diabetes associated with anger temperament after control for potential confounders including BMI and waist-to-hip ratio⁷¹. Studies on the role of hostility or anger in the aetiology of cardiovascular disease are more frequent and suggest an association^{72,73}, although one meta-analysis indicates that the effect is not that prominent¹¹⁰. The results in our study might reflect that individuals scoring low on a hostility scale express a lower neuroendocrine stress response^{111,112} which may be associated with a lower risk of developing type 2 diabetes¹¹³.

A decreased risk for having abnormal glucose regulation was demonstrated in men and women with high scores on the hedonic capacity scale. Hedonic capacity includes “positive emotionality”, and the ability to enjoy and be enthusiastic about everyday life⁸¹. The literature on hedonic capacity in relation to health outcomes is limited¹¹⁴. In one study of 10,308 civil servants in London, a measure of “positive affect” was not associated with coronary heart disease⁷⁵. In the present study, also low hedonic capacity in women was associated with abnormal glucose regulation, demonstrating an increased risk, although when the potential confounders were controlled for the association became non-significant. Scores on the lower range of the hedonic capacity scale intend to capture low mood, disengagement and feelings of helplessness. An increased risk for low hedonic capacity may correspond with that also depression⁹¹ and psychological distress¹¹⁵, has been shown to predict type 2 diabetes. However, the decreased risk in both men and women for having abnormal glucose regulation associated with high scores on hedonic capacity were more persistent after adjustment for confounders and could, like proposed for antagonism, operate through neuroendocrine stress systems, implying that individuals high on hedonic capacity, may express a lower stress response.

For the three other personality scales, there were no significant associations to abnormal glucose regulation in either men or women. The slightly reduced risk for low impulsivity in men, and over-risk for high negative affectivity in men, became non-significant after adjustment for BMI, FHD, smoking, physical activity, SEP

and psychological distress. It is however noteworthy, that negative affectivity, referring to an individual's susceptibility to negative emotions expressed as nervous tension and stress, most probably share features with, for example, the single question of anxiety that was prospectively associated with abnormal glucose regulation in our previous study¹¹⁵. The results from the present study refer to a narrowly defined personality trait and may be put in contrast to a single unvalidated question on symptoms on anxiety¹¹⁵. Different measures or concepts of personality, emotional stress or depressive symptoms may overlap in what they capture.

The selection of comparison group might influence the results. We used exposure scores around the mean as the reference. This is in accordance with the subscales being approximately normally distributed, and that scores around the mean are considered "normal" according to construction of the scales and theory in personality research. If you contrast the groups with extreme scores to each other, you may end up with stronger associations. Also, to estimate "overrisks" or "underisks" may be a matter of preference and is due to which exposure group is labelled as reference, i.e. having OR 1.0. If low antagonism is the reference, high antagonism may confer an overrisk, instead of low antagonism being "protective".

The point estimates were fairly robust after entering known confounding factors into the model which may be a sign of that they are distinct entities. Although BMI, that is a strong risk factor for type 2 diabetes was included among the potential confounders, the association between personality traits and abnormal glucose regulation were not changed.

Personality trait theory has a long tradition since the first documented person to suggest trait theory was Hippocrates (460-377 BC), describing humans having four basic fluids (or humors); yellow bile, blood, phlegm and black bile. Although a lot has happened to trait theory since then, traits are often referred to as "dispositions", capturing the idea that a person is predisposed to act in a certain way¹¹⁶. However, it has recently been emphasized that trait terms implicitly refer to behaviours in a type of social context¹¹⁷. One old critique of trait theory is its conception of humans being pre-disposed to act in certain ways. Our personalities are too dynamic to say that we have a high level of some specific trait. Individuals do not always act in the same way, it depends on the situation¹¹⁸. Another criticism has been that if trait theory offers no real guidance in the development of these traits, there is no strategy for helping someone to change. However, recent research stresses that personality does change, predominately in young adulthood (age 20-40)¹¹⁹.

5.1.4 Non-response

The main results of this study indicated the absence of non-response bias at the screening- and baseline steps of the SDPP study, since the absolute risks for non-responders/non-participants were equivalent to those for responders/participants, and accordingly, the ORs for non-responders/non-participants were not increased. In contrast, at the follow-up step, the risk for drug-treated diabetes was increased in non-participants compared to participants, suggesting that the sample had been subjected to some kind of selection towards healthier subjects.

Thereafter, we analysed the result in more detail for several of the type 2 diabetes risk factors measured at the baseline study. This evaluation suggested no false risk estimates for either men or women for FHD, smoking, physical activity, socio-economic position or psychological distress. For BMI though, the ORs illustrated separate patterns for men and women, and participation seemed to some extent to be selective in women, i.e. related to disease status within the BMI categories. This could lead to an overestimation of risk estimates associated with a high BMI.

The results also suggested that a higher proportion of all drug-treated diabetes cases among women than among men were non-participants, which probably means that a higher proportion of type 2 diabetes cases in women were not examined in the SDPP follow-up. If so, this may mirror the lower participation rate at the follow-up in women, 70% compared to men, 79%. It is also possible, that women who knew they had diabetes, i.e. had been diagnosed during the follow-up period, to greater extent declined to participate, compared to men. In addition, in women, BMI ≥ 30 , low physical activity, low SEP and high psychological distress were more prevalent at baseline among follow-up non-participants than among participants (Eriksson et al). Current smoking was more prevalent in non-participants in both men and women. At the same time, despite adjustment for these potential confounders, the elevated risk for drug-treated diabetes in non-participants at follow-up persisted, in both men and women. This may be due to other unmeasured factors which increase the risk for diabetes in our non-participants.

In conclusion, this evaluation with the Swedish Prescribed Drug Register supports the hypothesis that non-response bias is not a problem in the SDPP study at screening and baseline steps. This suggests that diabetes prevalence and risks may be estimated from a population-based cohort study on type 2 diabetes with high participation rate, such as the SDPP. However, a potential problem may exist in the follow-up step, because after having performed several steps the sample may have been subjected to selection bias. Hence, follow-up data should be interpreted with some caution. The overall lower response rate at follow-up in women, and presumably higher proportion of missed cases points to the importance of motivating women to participate in a diabetes health exam.

5.2 METHODOLOGY

5.2.1 Study design

SDPP is a population-based cohort study. The second and fourth papers in this thesis were incidence studies taking advantage of the prospective design which render possible causal interpretation. The first and third studies were cross-sectional studies where the exposure and disease are measured at the same point in time. This implies that any temporal relationship is impossible to assess. However, all prevalent cases of type 2 diabetes were excluded prior to the baseline study. This makes it less likely that changes in habits or symptoms (smoking, physical activity, psychological distress), or recall bias of exposure levels, occurred in this group as a result of knowledge of disease. For the same reason, only the subjects that were classified with normal glucose tolerance at baseline were included in the prospective analyses in the second and fourth papers. (The individuals with pre-stages were informed to contact their primary health care centre for help with life

style changes, and individuals diagnosed with type 2 diabetes were referred to a physician for treatment).

5.2.2 Misclassification of disease

Glucose tolerance in the SDPP was measured by screening with OGTT. This is an advantage compared to self-report, making it possible also to include previously undiagnosed cases of type 2 diabetes and pre-diabetes which otherwise will be missed. Such under-diagnosing can be substantial, for two diagnosed cases there will be one undiagnosed¹¹. Since the individuals with known type 2 diabetes were excluded prior to baseline and follow-up, it is possible that we have been studying less intense, essentially symptoms-free forms of type 2 diabetes. However, there is no evidence that the aetiology of milder type 2 diabetes would differ from more severe cases. On the other hand, the exclusion of the prevalent cases may entail that individuals particularly vulnerable to the studied exposures have been sorted out possibly leading to an underestimation of the studied associations.

In the fourth study, the non-response analysis, type 2 diabetes was measured as filled prescriptions of anti-diabetic drugs recorded in the Swedish Prescribed Drug Register. The advantage of this measure was the possibility to estimate the disease risk for the entire original SDPP cohort, including the non-participants. The complete accuracy of anti-diabetic drugs as a measure of type 2 diabetes can be questioned. There will be under-diagnosing of cases treated with diet only, about 25%, and the register also lacks information of unknown cases of type 2 diabetes. However, the participants in SDPP are already screened for unknown type 2 diabetes, so under-diagnosing should not be considerable in this group. Moreover, as long as misclassification is not related to exposure, which it should not be in this case, a crude method for identification of cases will not result in spurious associations. Even though the diabetes cases in the SDPP cohort drawn from the Swedish Prescribed Drug Register were treated with anti-diabetic drugs including insulin, they were not likely to have type 1 diabetes since all individuals with diabetes were excluded prior to the SDPP baseline study. In addition, it is reasonable to assume that only few of those who developed diabetes during the follow-up period have type 1 diabetes, considering their age (above 35 years at baseline). We can not rule out that some of our cases have latent autoimmune diabetes in the adult (LADA) since anti-GAD were not analysed. LADA amounts to 5-10% of all diabetes and a criteria is a disease debut above 30-35 years of age⁴. Although characterised by autoimmunity to betacells like type 1 diabetes, it has been shown that LADA share risk factors such as FHD¹²⁰, overweight, low physical activity and increasing age¹²¹ with type 2 diabetes.

5.2.3 Misclassification of exposure

Most lifestyle exposures were self-reported and evaluated from questionnaires, and this may introduce bias, due to misclassification. The personality instrument has been evaluated with regard to reliability and validity with satisfactory results, partly on the present data cohort^{81,82}. Also, measurement of personality ought not to introduce recall bias, since it is intended to capture a more regular personal pattern of behaviour or attitudes. The psychological distress index was not a validated instrument, although showed adequate reliability according to the Cronbach's

alpha. We also analysed the separate questions included in the index, for clarification. The different results in men and women is perhaps most striking, and since validation is lacking it can't be excluded that the instrument measures different things in men and women, although the level of symptoms reporting is in line what have previously been found. However, since men and women were compared within gender, it is not likely that in between gender differences explain the association observed in men or women. The scale of SOC was a short version reported to be adequately valid⁸⁰. However, as already stated, an obvious advantage was that the participants were not aware of their glucose status at the baseline health examination when answering the questionnaire, thereby making differential misclassification (in the group with disease and the group without disease) with regard to psychological distress, personality, smoking, physical activity, and SOC less likely.

5.2.4 Selection

The study sample in the SDPP was restricted to Swedish-born individuals, and half of the participants had a family history of diabetes and half had not. All individuals that had an unclear or insufficient family history of diabetes were excluded. The reason for applying the inclusion and exclusion criteria was to enrich the study population with regard to family history of diabetes in an ethnically relatively homogenous population, for the purpose of studying the impact of family history on type 2 diabetes. The self-reported prevalence of a family history of diabetes was originally 22-25%. By the enrichment, the prevalence became 50%. Theoretically, the enrichment of a family history of diabetes would have caused a higher prevalence of type 2 diabetes in our study group, since family history of diabetes is a risk factor. However, the sole impact of a family history of diabetes is not that great. Other factors are involved: some of them having an even stronger influence on type 2 diabetes, like BMI. In addition, other circumstances may influence the prevalence of type 2 diabetes in the response- and non-response groups; for instance, the non-response group could have other diseases (that the responders do not have) that made them unwilling to participate, and which increases their risk for type 2 diabetes. We do not know the prevalence of a family history of diabetes in non-responders at the screening phase.

In study IV, it was indicated that selective non-response was not present at the screening- and baseline steps since the prevalence of drug-treated diabetes was equal in responders and non-responders, while at follow-up selection bias to some extent seemed to have been introduced.

5.2.5 Confounding

An advantage in the present studies was that we had the opportunity to take many potential confounders into account. However, it is not possible to know if there are factors involved which are not measured (residual confounding). When studying the associations between exposures and disease, a confounder is a factor that is also associated with the disease. In addition, the confounder must be related to the exposure, however should not be an effect of the exposure³⁸.

5.3 GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Extensive cohort and diabetes screening studies are costly to perform. However, screening leading to early diagnosis of diabetes is important, as early treatment reduces the risk of complications. In addition, etiological studies that can be carried out reveal insights in which factors or exposures that influence the risk of developing type 2 diabetes. This thesis demonstrates that initiatives such as the Stockholm Diabetes Prevention Program generates knowledge and most important, that the problem of non-response seems practically negligible. The SDPP forms a solid base for research which can be used to identify risk groups and design interventions that may be applied on different levels in society.

Examples of further studies:

- Evaluation of biologic interaction effects between risk factors for type 2 diabetes, using a prospective approach.
- Analyses of psychological distress and depression influencing the risk of type 2 diabetes, using validated instruments and taking into account duration of exposure, and if possible also sleep quality and quantity.
- Studies identifying the biological mechanisms linking depression and sleep disturbances to type 2 diabetes.
- Examination and follow-up of women with gestational diabetes.
- Assessment of diabetes in non-European immigrants in Sweden and their specific risk factors, and possible prevention strategies.

6 CONCLUSIONS

This thesis provides additional insights into the aetiology of type 2 diabetes in Swedish middle-aged men and women. The thesis confirms that a family history of diabetes is an important risk factor in men and women and that family history of diabetes does not obviously act in biologic synergy with other risk factors such as increased BMI, smoking or physical inactivity, or low sense of coherence. There is cross-sectional interaction between family history of diabetes and BMI in women.

The studies also add to the accumulating evidence that psychological distress, in our study measured as self-reported symptoms of anxiety, apathy, depression, fatigue and insomnia, plays a role in the aetiology of type 2 diabetes, at least in men.

The results suggest that personality factors may be associated with abnormal glucose regulation such as antagonism in men, and hedonic capacity in men and women, while others, such as impulsivity, negative affectivity, and alexithymia may not be associated with abnormal glucose regulation.

In addition, the thesis demonstrates that a population-based cohort study on type 2 diabetes including screening with OGTT, with high attendance rates, seems to provide accurate information regarding the prevalence at screening and baseline steps, however at follow-up, after having performed several steps, the sample may have been subjected to selection bias influencing the cumulative incidence. However, the effect of this in the association studies seems to be fairly limited.

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