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WEIGHT HISTORY, LOW BIRTH WEIGHT, ALCOHOL CONSUMPTION AND TYPE 2 DIABETES

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Till Elsa och Peter
All men are mortal.
Socrates was mortal.
Therefore, all men are Socrates.
W.A.
ABSTRACT

Type 2 diabetes is an increasing public health problem, currently affecting about 3-4% of the Swedish population. Better knowledge about etiologic factors may lead to more specific intervention and prevention of the disease. The aim of this thesis was to contribute to this knowledge by investigating the association between type 2 diabetes and weight history, low birth weight and alcohol consumption.

Analyses were based on a cross-sectional study consisting of 3128 middle-aged men of whom 50% had diabetes in close relatives (Stockholm Diabetes Prevention Program (SDPP)). During a health examination, 55 cases of type 2 diabetes and 172 cases of impaired glucose tolerance (IGT) were identified by oral glucose tolerance test. In addition, information on previous weight, birth weight, alcohol consumption and other lifestyle factors were obtained by questionnaire. Analyses of alcohol and type 2 diabetes were also performed in a large prospective study based on the Finnish Twin Cohort. This Cohort was compiled in 1974 and consists of about 16,000 twin pairs. In 1975, 1981 and 1990, subjects were investigated by questionnaire on health and lifestyle factors, including alcohol. By record linkage to registers of hospital discharge and prescribed medication we identified incident cases of diabetes 1976-1995. A clinical study performed within the Cohort was used to investigate the validity of questionnaire information on alcohol. In this study, information on alcohol by questionnaire, by interview and through three biochemical indicators of alcohol intake; CDT, gamma-GT and MCV was obtained for a sub-sample of 76 twin pairs.

The results indicated that the prevalence of type 2 diabetes and impaired glucose tolerance increases with duration of obesity. The odds ratio (OR) of diabetes associated with a short (<5 years) and long (>10 years) duration of overweight (BMI>25.0 kg/m²) was estimated at 1.9 (95% confidence interval (CI)=0.5-7.1) and 7.3 (95% CI=2.2-23.7), respectively. Low birth weight (<3000g) was associated with an increased prevalence of diabetes (OR=4.5, 95% CI=1.9-10.8) and of IGT (OR=1.9, 95% CI=1.0-3.4) after adjustment for family history of diabetes. In men with a family history of diabetes in combination with low birth weight the odds ratio of diabetes was 10.9 (95% CI=2.9-41.2).

Results from SDPP and from the Finnish Twin Cohort were compatible with a reduced risk of diabetes in moderate consumers of alcohol among men, OR=0.7, 95% CI=0.3-1.8, and RR=0.7, 95% CI=0.5-1.1, respectively. High alcohol intake was associated with an increased prevalence of diabetes in men of SDPP (OR=2.1 (95% CI=1.0-4.5) but not in the Finnish Twin Cohort. Binge drinking in women of the Finnish Twin Cohort was associated with an increased risk (RR=2.1, 95% CI=1.0-4.4).

Comparison of questionnaire information on alcohol to dietary interview information and biochemical indicators indicated that the questionnaire had a rather low sensitivity but high specificity for identification of high consumers.

In conclusion, the results of this thesis suggest that a long duration of obesity is an important risk factor for type 2 diabetes in addition to degree and distribution of obesity. The results are also consistent with previous studies, indicating that low birth weight is associated with type 2 diabetes. Furthermore, the results suggest that men with the combination of low birth weight and family history of diabetes may be particularly prone to develop the disease. Results from this thesis also provide support for the hypothesis that moderate alcohol consumption reduces the risk of type 2 diabetes.
LIST OF PUBLICATIONS


CONTENTS

INTRODUCTION ................................................................................................. 1

TYPE 2 DIABETES .......................................................................................... 1

RISK FACTORS ............................................................................................ 1

General ......................................................................................................... 1

Obesity ......................................................................................................... 2

Low birth weight ....................................................................................... 2

Alcohol consumption ............................................................................ 3

AIMS OF THE THESIS .................................................................................. 7

MATERIALS AND METHODS ...................................................................... 9

FINNISH DIABETES PREVENTION PROGRAM, PAPER I-III ....................... 9

Study population ....................................................................................... 9

Health examination ................................................................................... 13

Classification of glucose tolerance ......................................................... 13

Classification of insulin resistance and secretion .................................. 14

Classification of exposure ....................................................................... 14

Data analysis ............................................................................................ 15

FINNISH TWIN COHORT - PAPER IV ............................................................... 16

Study population ....................................................................................... 16

Clinical examination .............................................................................. 16

Questionnaire ........................................................................................ 17

Dietary history interview ....................................................................... 17

Data analysis .......................................................................................... 18

FINNISH TWIN COHORT - PAPER V ............................................................... 18

Study population ....................................................................................... 18

Classification of exposure .................................................................... 18

Classification of diabetes .................................................................... 19

Data analyses ........................................................................................ 20

RESULTS ....................................................................................................... 21

FINNISH DIABETES PREVENTION PROGRAM ........................................... 21

Paper I- Weight history ......................................................................... 21

Paper II- Low birth weight ................................................................. 23

Paper III- Alcohol consumption and prevalence type 2 diabetes ....... 23

FINNISH TWIN COHORT ............................................................................. 24

Paper IV- Questionnaire information on alcohol consumption ....... 24

Paper V- Alcohol consumption and incidence of type 2 diabetes ...... 25

DISCUSSION .................................................................................................. 27

RESULTS ....................................................................................................... 27

Weight history .......................................................................................... 27

Low birth weight .................................................................................... 27

Alcohol consumption ........................................................................... 28

METHODOLOGY ........................................................................................... 30

Study design ............................................................................................ 30

Misclassification of disease .................................................................. 30

Misclassification of exposure ............................................................... 31

Selection .................................................................................................. 32
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CDT</td>
<td>Carbohydrate Deficient Transferrin</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>fl</td>
<td>Femtolitre</td>
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<tr>
<td>Gamma-GT</td>
<td>Gamma Glutamyltransferase</td>
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<tr>
<td>IGT</td>
<td>Impaired Glucose Tolerance</td>
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<tr>
<td>MCV</td>
<td>Mean Corpuscular Volume</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose Tolerance</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>U/L</td>
<td>Units per Liter</td>
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<td>WHO</td>
<td>World Health Organization</td>
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INTRODUCTION

Type 2 diabetes is a common chronic disease in the Western world with a prevalence of about 3-4% in Spain. The disease is becoming an increasing public health problem as studies indicate that the prevalence has increased during the last decades and that this is a continuing trend. This development can only in part be explained by demographic transitions, better diagnostic criteria and treatment. In addition, the westernised lifestyle characterized by low physical activity, by intake of a high fat and low fibre diet and by obesity, is likely to be important. With levels of obesity rising worldwide, it is reasonable to expect the prevalence of type 2 diabetes to increase further. This is an alarming development that calls for effective preventive strategies. A better understanding of etiologic factors may lead to more specific intervention and possibly to prevention of the disease.

TYPE 2 DIABETES

Type 2 diabetes is the most common form of diabetes, accounting for 80-90% of all cases. The prevalence varies greatly between different parts of the world ranging from about 3% in Europe, to more than 40% in Pima Indians in Arizona. In addition, in Sweden about 10-15% of the middle-aged population is estimated to have impaired glucose tolerance. This is not a disease but a condition which increases the risk of developing diabetes 6-10 times.

All forms of diabetes result by definition from an inability of the body to sustain glucose levels. This inability results from an imbalance between insulin sensitivity and secretion. The mechanisms responsible for type 2 diabetes include β-cell dysfunction, affecting insulin secretion, and insulin resistance. Insulin resistance is often the most obvious abnormality in type 2 diabetes impairing the body’s ability to respond to insulin. This impairment affects insulin sensitive tissues, mainly muscle, liver and adipose tissue. The body compensates for decreased insulin sensitivity by increasing insulin secretion. However, with time, the β-cells fail to maintain this high insulin secretion and eventually manifest diabetes results.

RISK FACTORS

General
Type 2 diabetes has a familial distribution generally believed to be the result of shared environment as well as genes. Studies have indicated that the occurrence of diabetes in persons with close relatives with the disease is increased in the order of 2-4 times. A
genetic explanation is primarily supported by twin studies that demonstrate a concordance rate of 60-80% in monozygotic twins \(^{10}\). Environmental factors are also strongly related to the occurrence of type 2 diabetes. The most well known are obesity and physical inactivity but other lifestyle factors such as diet, smoking and alcohol consumption have also been suggested as important determinants. Furthermore, it is generally considered that environmental factors act on genetic predisposition to promote diabetes \(^{15}\). Information on family history of diabetes is therefore important to take into account when investigating relationships between environmental factors and diabetes. The interplay between hereditary and environmental factors in the aetiology is also an important field of study.

**Obesity**

Obesity is the most well recognized risk factor for type 2 diabetes. Numerous studies have demonstrated a dose-response relationship between degree of obesity and glucose intolerance. For example, in a previous Swedish study the relative risk of diabetes was 21.7 in men with a body mass index in the highest quintile compared to men in the lowest quintile \(^{14}\). A central distribution of obesity has been indicated to have a particularly detrimental effect on the risk of diabetes \(^{17}\). In addition, it has been suggested that duration of obesity influences the risk of diabetes \(^{18-19}\). In a Pima Indian study, subjects with a body mass index over 30 since more than 10 years had 2.5 times higher incidence of diabetes, compared to subjects with the same level of obesity since less than five years \(^{19}\). However, the influence of duration of obesity is not fully understood. Although it is well known that the presence of obesity increases the risk of diabetes by way of insulin resistance \(^{16}\), the effects of duration of obesity on insulin sensitivity and secretion are less clear. In the Pima Indian study, the results indicated that after a long duration, obesity was associated with reduced insulin secretion rather than insulin resistance \(^{19}\). It is however uncertain if results from a high prevalence population such as the Pimas can be extrapolated to low prevalence populations.

**Low birth weight**

In the early 1990s Barker and colleagues reported an association between low birth weight and development of several degenerative diseases including high blood pressure, cardiovascular disease and type 2 diabetes \(^{11}\). Since then this association has been confirmed in many different populations including British, Swedish, Mexican-American and Pima Indian \(^{17}\). The findings have generated the thrifty phenotype hypothesis, which proposes that these diseases originate from permanent effects of fetal malnutrition \(^{17}\). Nevertheless, a possible influence of hereditary factors on the relationship between birth weight and glucose
tolerance cannot be ruled out. It seems plausible that a diabetic genotype, in addition to increasing the risk of type 2 diabetes, could affect fetal growth.

**Alcohol consumption**

The influence of alcohol consumption on glucose tolerance is not clear. A protective effect of moderate drinking has been shown in several studies\(^{24-32}\) (Figure 1). Together with results indicating an increased risk in high consumers\(^{24-27, 33-34}\) the results seem to suggest a U-shaped relationship between alcohol consumption and type 2 diabetes (Figure 2). On the other hand, a number of studies did not find an association between high alcohol intake and type 2 diabetes\(^{28-32, 35-37}\). Notably, an increased risk in high consumers has only been seen in men\(^{24-27, 33-34}\) whereas the studies of women indicate a protective effect\(^{27, 32}\) or a lack of association between alcohol intake and diabetes\(^{33-34, 36-37}\). Only two studies have investigated the influence of alcohol consumption on the risk of impaired glucose tolerance\(^{35-36}\) and the results of these studies were not consistent. With regard to the influence of different aspects of alcohol intake besides amount consumed such as type of drink or binge drinking this has only been investigated to a limited extent.

Alcohol intake will affect metabolism in many different ways and both negative and positive effects on mechanisms related to glucose homeostasis have been suggested. It has been shown that intake of alcohol may enhance insulin sensitivity\(^{38, 39}\). On the other hand, experimental studies of the effect of acute alcohol intake have indicated an association with enhanced insulin release and either reduced\(^{40-42}\) or unchanged glucose tolerance\(^{43}\). Also, repeated large doses of alcohol have been shown to be capable of producing reversible insulin resistance\(^{44-45}\). A diabetogenic influence could also be exerted by a toxic effect on the pancreas\(^{46}\), or indirectly by increased adiposity\(^{47, 48}\). In heavy drinkers, diabetes may be secondary to reduced insulin secretion associated with chronic pancreatitis\(^{48}\) or insulin resistance associated with alcohol induced liver changes\(^{49}\).

Discrepant results of previous studies on high alcohol intake and type 2 diabetes could perhaps in part be explained by the difficulty in assessing alcohol intake. Most studies have used questionnaire information on alcohol. This method is generally afflicted with underreporting\(^{50}\). The rationale for using questionnaire information in spite of this underreporting is that it is assumed to have only a minor effect on ranking. However, a major limitation in most studies investigating the validity of questionnaire information on alcohol is the use of other self-report methods as reference, such as 7-day dietary records and diet history interviews\(^{52-54}\). These methods may be afflicted with the same type of underreporting.
as the questionnaire. An alternative approach is to use biochemical indicators of alcohol intake. At present there are no good indicators of alcohol intake in the low to moderate range but there are established indicators of chronic high alcohol intake\textsuperscript{35}.

**Figure 1.** Relative risk of type 2 diabetes together with 95% confidence intervals in men with moderate compared to low alcohol consumption. Results of some previous studies.\textsuperscript{a}

\textbf{Wannamethee:} 15-42 drinks/week vs. \(<1\) drink/week. \textbf{Conigrave:} 15-29g/day vs. abstainers. \textbf{Tsumura:} 29.1-50.0 ml/day vs. abstainers, \textbf{Todoroki:} 30-59 ml/day vs. abstainers, \textbf{Kao:} 7.1-14 drinks/week vs. \(\leq 1\) drink/week, \textbf{Ajani:} \(\geq 1\) drink/day vs. rarely/never. \textbf{Perry:} 16-42 units/week vs. \(<1\) unit/week.

\textsuperscript{a} All epidemiological studies on the association between moderate alcohol intake and type 2 diabetes in men are not included because relative risk estimates were not available in some studies: de Vegt 2002, Holbrook 1990, Hodge 1993, Nakanishi 2003, Monterossa 1995, Wei 2000
Figure 2. Relative risk of type 2 diabetes together with 95% confidence intervals in men with high compared to low alcohol consumption. Results of some previous studies.†

Wannamethee: >42 drinks/week vs. <1 drink/week. Conigrave: ≥50g/day vs. abstainers. Tsumura: >50.0 ml/day vs. abstainers. Todoroki: ≥60ml/day vs. abstainers. Kao: >21 drinks/week vs. ≤1 drink per week. Wei: >39.5g/day vs. 8.8-17.5g/day. Holbrook: >25g/day vs. ≤25g/day. Nakanishi: ≥69g/day vs. 23-45.9g/day.

† All epidemiological studies on the association between high alcohol intake and type 2 diabetes in men are not included because relative risk estimates were not available in some studies: Ajani 2000, de Vegt 2002, Hodge 1993, Monterossa 1995, Perry 1995.
AIMS OF THE THESIS

- To study the association between weight history and glucose intolerance and long-term effects of obesity on insulin resistance and secretion.

- To study the association between low birth weight and glucose intolerance in relation to family history of diabetes.

- To study the association between alcohol consumption and type 2 diabetes and impaired glucose tolerance, respectively.

- To evaluate self-reported questionnaire information on alcohol consumption.
MATERIALS AND METHODS

STOCKHOLM DIABETES PREVENTION PROGRAM, PAPER I-III

Study population
The analyses of papers I-III were based on a cross-sectional study of 3128 men in the age’s 35-56 years, of which 50% had diabetes in the family. The study population were residents of four suburban municipalities in the Stockholm County: Sigtuna, Tyresö, Upplands-Bro and Värmö in 1992. In the general Swedish population about 15-20% have close relatives with diabetes. To obtain a sample where half the participants had diabetes in the family, thereby improving our possibilities of accounting for family history, the sample was collected in two steps (Figure 3). First, all men born 1938-1957 and living in one of the four municipalities received a one-page postal questionnaire in 1992, asking about country of birth and if he himself or close relatives had diabetes. Of 12952 subjects, we obtained completed questionnaires from 10236 (79%) after up to two reminders by mail. Among those who responded we identified 2106 (20.6%) subjects with family history of diabetes, defined as at least one first degree relative (mother, father, sister or brother) or two second degree relatives (grandparents, uncles or aunts) with diabetes. Furthermore, we identified 3329 (32.5%) subjects without diabetes in the family; that is to say they had neither first nor second-degree relatives, nor cousins with known diabetes. There were 1531 (15.0%) men with insufficient family history of diabetes according to our inclusion criteria (i.e. diabetes in a more distant relative) and 2800 (27.4%) men who were unable to give complete answers regarding family history. These two latter groups of men were excluded along with 258 (2.5%) persons who reported known diabetes and 212 (2.1%) persons who reported foreign origin.

In a second step, all men with a family history of diabetes, along with an age-matched sample of subjects without family history of diabetes, were invited to participate in a health examination at a primary health care centre. In total, 70% agreed to participate. During the visit at the health care centre, family history of diabetes was investigated once again. As a result of this second inquiry, another 33 persons turned out to have an insufficient family history of diabetes according to our inclusion criteria and were therefore excluded. One person did not complete the glucose tolerance test. The final study group consisted of 3128 persons.
Through record linkage to the 1990 Swedish census we collected information on income, education, socio-economic status and country of origin for all the men eligible for the study. This information was used to investigate if participants were systematically different from non-participants with regard to income, education and socio-economic status.
Figure 4. Study population and participants in the Stockholm Diabetes Prevention Program by income

In the above figure, subjects are divided into tertiles according to the income distribution of the study population. From the figure it is evident that among participants the proportion of subjects with low income was lower and the proportion with high income higher than in the study population. It can also be seen that participants without family history of diabetes on average had higher income than participants with diabetes in the family. More than 40% of participants without family history of diabetes were in the high-income group compared to 33% of the source population. The same patterns were seen for education and socio-economic class; on average participants tended to have higher education and socio-economic status, particularly participants without family history of diabetes (Figure 5 and 6).
Figure 5. Study population and participants in the Stockholm Diabetes Prevention Program by education

Figure 6. Study population and participants in the Stockholm Diabetes Prevention Program by socio-economic status
Health examination
The health examination included an oral glucose tolerance test according to WHO standards. In addition, measures of height, weight, waist-, hip circumference and blood pressure were obtained. During the visit at the health care centre the participants also completed an extensive questionnaire covering information on weight history, birth weight, alcohol consumption, tobacco use, dietary habits, physical activity, health status and psychosocial conditions.

Classification of glucose tolerance
Diabetes was defined according to WHO 1985 criteria as 2h plasma glucose levels from 11.1 millimol/liter (mM) and impaired glucose tolerance as levels between 7.8-11.0 mM. The number of subjects with impaired glucose tolerance and type 2 diabetes is shown in table 1. In paper II a third glucose tolerance group was included, consisting of 57 subjects with impaired fasting glucose according to the new classification by the American Diabetes Association (ADA), defined as fasting plasma glucose levels between 6.1-6.9 mM.

Table 1. Number of subjects with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes by age, family history and body mass index.

<table>
<thead>
<tr>
<th></th>
<th>Normal glucose tolerance</th>
<th>Impaired glucose tolerance</th>
<th>Type 2 diabetes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-45</td>
<td>1132 (94.8%)</td>
<td>53 (4.4%)</td>
<td>9 (0.8%)</td>
<td>1194</td>
</tr>
<tr>
<td>46-56</td>
<td>1769 (91.5%)</td>
<td>119 (6.2%)</td>
<td>46 (2.4%)</td>
<td>1934</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1437 (95.4%)</td>
<td>60 (4.0%)</td>
<td>10 (0.7%)</td>
<td>1507</td>
</tr>
<tr>
<td>Yes</td>
<td>1464 (90.3%)</td>
<td>112 (6.9%)</td>
<td>45 (2.8%)</td>
<td>1621</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24.9</td>
<td>1241 (97.5%)</td>
<td>20 (1.6%)</td>
<td>12 (0.9%)</td>
<td>1273</td>
</tr>
<tr>
<td>25.0-27.9</td>
<td>1013 (93.4%)</td>
<td>57 (5.3%)</td>
<td>15 (1.4%)</td>
<td>1085</td>
</tr>
<tr>
<td>≥28.0</td>
<td>639 (83.9%)</td>
<td>95 (12.5%)</td>
<td>28 (3.7%)</td>
<td>762</td>
</tr>
<tr>
<td>Total</td>
<td>2901 (92.7%)</td>
<td>172 (5.5%)</td>
<td>55 (1.8%)</td>
<td>3128</td>
</tr>
</tbody>
</table>

13
Classification of insulin resistance and secretion

Subjects with impaired glucose tolerance were classified according to estimated degree of insulin resistance and insulin deficiency based on measures of 0 and 2h insulin levels taken during the oral glucose tolerance test. To improve reliability we employed two different methods to define each dysfunction. First we defined subjects with impaired glucose tolerance and fasting insulin concentrations in the highest tertile (≥30.0mU/l) as insulin resistant and men with a 0 to 120 min rise of insulin in the lowest tertile (≤71.9 mU/l) after glucose load, as low insulin responders. Subjects who belonged to both categories (n=7) were excluded from the analyses. As an alternative method, we calculated insulin resistance and secretion based on the relationship between fasting levels of glucose and insulin with the HOMA (HOMoeostasis Model Assessment) model37 according to published algorithms: HOMA (resistance)= (insulin*glucose) and HOMA (β-cell function) = (insulin/glucose-3.5)57-58. Subjects with impaired glucose tolerance belonging to the highest tertile on the HOMA (insulin resistance) parameter were arbitrarily defined as insulin resistant (≥161.1). Those with HOMA (β-cell function) values in the lowest tertile (≤11.2) were defined as having relatively low insulin secretion. Seven men belonging to the highest tertile on the HOMA (resistance) parameter as well as the lowest tertile on the HOMA (β-cell function) parameter were excluded from the analyses.

Classification of exposure

Weight history

The measure of duration of obesity used in paper I was based on measures of height and weight from the health examination together with self-reported information on weight five and 10 years earlier. Current body mass index was calculated from weight and height measured at the health examination and body mass index five and 10 years ago was estimated using height from the health examination together with self-reported information on weight from the questionnaire. Overweight was defined as body mass index (kg/m²) from 25.0 and over. In the analyses of duration of obesity, subjects with a body mass index of 25 or more for at least 10 years, for at least 5 years but not 10 years, and currently but not five or 10 years earlier, were compared to subjects with a body mass index of less than 25.0 at all three points in time.

Birth weight

Self-reported information about birth weight was obtained from the questionnaire. In the analyses we used arbitrarily defined categories of birth weight: ≤3000g, 3001-3600g and ≥3600g. 2237 (71.5%) subjects reported complete information about birth weight. Therefore.
the analyses of birth weight were based on fewer subjects than the analyses in papers I and III.

Alcohol consumption
In the questionnaire subjects were asked about their current consumption of beer, wine, dessert wine and liquor, respectively. For each type of beverage, there were questions about the frequency as well as the amount consumed at each occasion. Based on these questions the total current alcohol consumption in terms of 100% alcohol on average per week was calculated. The estimated contents of 100% alcohol per ml were 0.05 ml for beer, 0.12 ml for wine, 0.19 ml for dessert wine and 0.4 ml for liquor. In the analyses, subjects were categorized into quartiles according to the reported total weekly 100% alcohol consumption: (occasional; <60.2, low; 60.2-116.6, moderate; 116.7-201.5 and high; ≥201.5 ml 100% alcohol per week. To allow for separate analyses for type of beverage, subjects were also classified separately according to their intake of alcohol from wine, beer and spirits (<10ml, 10-39.9ml, 40-79.9ml and ≥80ml 100% alcohol per week). From the analyses we excluded 116 subjects due to missing data on alcohol consumption and 100 abstainers. Abstainers were excluded since this group may include subjects with previous high consumption of alcohol or medical conditions preventing them from drinking.

Data analysis
The basic aim of the data analyses was to compare the prevalence of diabetes and impaired glucose tolerance between exposed and unexposed subjects. To estimate the prevalence rate ratios we calculated odds ratios. We found this justified in view of the low prevalence of the main outcomes. The prevalence odds ratios together with 95% confidence intervals were estimated using multiple logistic regression analysis. Confounding was adjusted for in the analyses of weight history in paper I by including current weight, family history of diabetes, physical activity and age in the logistic regression model. In the birth weight analyses (paper II) we adjusted for family history of diabetes, body mass index, socio-economic affiliation of the father and age. Furthermore, in paper III the alcohol consumption analyses were adjusted for body mass index, smoking, physical activity, socio-economic affiliation and age. In addition, data were stratified by family history of diabetes. All analyses were performed using the SAS/STAT statistical package, release 6.12.
FINNISH TWIN COHORT - PAPER IV

Study population
The Finnish Twin cohort was compiled in 1974 and includes in all about 16,000 same-sexed twin pairs who were born in Finland before 1958 where both twins were alive in 1967. In 1998 a small clinical study was performed within the Cohort. The major purpose of this study was to investigate the risk of cardiovascular disease in emigrants from Finland to Sweden. All twin pairs in the Finnish Twin cohort where one twin had moved to Sweden and the co-twin remained in Finland were identified (n=1,089 twin pairs). A sub-sample of these twins was selected to take part in a clinical examination focusing on early signs for arteriosclerosis and risk factors for cardiovascular disease. This sub-sample consisted of male twin pairs, 40-70 years of age, where the migrant had lived at least 20 years in Sweden and the co-twin had always lived in Finland. In all there were 194 twin pairs eligible for participation and 122 of these pairs were selected to take part in the study, including all monozygotic twins and dizygotic pairs preferably born in east Finland. Of those selected, 19 pairs could not be contacted because of lack of address and/or telephone number and two pairs were excluded because one in the pair had deceased and another pair because they were found not to be twins. Of remaining 100 pairs, 76 complete pairs participated in the examination.

Clinical examination
The clinical examination was carried out between January 1998 and January 1999 at the Research Centre of the Social Insurance Institution and the Department of Medicine, Turku University Central Hospital, both in Turku, Finland. As a rule, both twins of a pair were examined on the same day. Both twins spent the night at the Social Insurance Institution and instructed to refrain from alcohol during the 24 hours preceding the examination. At the clinical examination, venous blood samples were collected after an overnight fast. Carbohydrate deficient transferrin (%CDT) was analysed with turbidimetric immunoassay (Bio-Rad Diagnostics, Hercules, California, USA). Serum gamma glutamyltransferase (gamma-GT) was measured with a kinetic method according to European Committee for Clinical Laboratory Standards (ECCLS) guidelines. Mean corpuscular volume (MCV) was determined from EDTA blood with an automatic cell counter (Coulter TC-10, Luton, England). To identify high consumers a cut-off point of ≥6 % were used for CDT as suggested by the manufacturer of the test. For gamma-GT we used the cut-off ≥80 U/l as recommended by ECCLS. With regard to MCV we arbitrarily chose a value of ≥96 fl to identify high consumers as there is no generally agreed cut-off point and values from 90-100
fl have been suggested. Height and weight were also measured. Based on these measures we calculated body mass index (kg/m²).

**Questionnaire**
After confirming their participation in the clinical examination, subjects received and filled out an extensive questionnaire at home, which they turned in upon arrival in Turku. The questionnaire included questions on alcohol consumption, smoking, health, physical activity, diet and socio-economic conditions. With regard to alcohol, there were separate questions on quantity of beer, alco-pops, wine, dessert wine and spirits used during an average week or month. Quantity was measured on three 7-point scales, with the upper limits defined as consuming ≥48 bottles of beer per week, ≥48 bottles of alco-pops per week, ≥10 bottles of wine per week, ≥8 bottles of dessert wine per week or ≥20 bottles of spirits per month, as used in earlier studies of the Finnish Twin Cohort Study. For each type of beverage, consumption was converted into grams of absolute alcohol and summed to yield an estimate of total alcohol consumption in grams per day. Subjects were divided into four consumption groups according to their intake of the five beverages as reported in the questionnaire: (1) Abstainers, (2) light consumers (<20 g alcohol per day), (3) moderate consumers (20-29.9 g alcohol per day) and (4) high consumers (≥30 g alcohol per day) (10 g corresponding to one standard drink). In addition, subjects were asked if they ever consumed more than 5 bottles of beer, one bottle of wine or 4 drinks (≥18 cl spirits) at one occasion with the response options: yes/no and how often they did this: “daily”, “2-4 times per week”, “once a week”, “2-3 times per month”, “once a month”, “2-6 times per year” and “more seldom”. Subjects were also asked to agree or disagree with the statement “I have or have had drinking problems” with the response options: “do not agree at all”, “do not agree”, “agree somewhat” and “agree”.

**Dietary history interview**
At the clinical examination an experienced nutritionist performed a detailed dietary history interview, which dealt with the subjects’ normal diet during the past year. During the interview, subjects were asked about the frequency and quantity of alcoholic beverages consumed during an average day, week, month or year. Questions were asked separately for beer, alco-pops, red and white wine, different types of liquor (whisky, gin, cognac, liqueur, vodka, gin) and dessert wine (sherry, vermouth). To calculate total alcohol consumption per day we converted each item into 100% alcohol and combined them to an estimate of total alcohol consumption in grams per day. For the analyses subjects were classified as
abstainers, light, moderate and high consumers. The classification was the same as the classification used for the questionnaire information.

Data analysis
To determine the correspondence between self-reported alcohol information and the biological indicators, differences in mean levels of CDT, gamma-GT and MCV between questionnaire and interview based consumption groups were analysed by one-way analysis of variance. Furthermore, correlations between CDT, gamma-GT and MCV levels and self-reported alcohol intake in grams per day were assessed using Spearman rank correlation coefficient. The standard errors and p-values from these analyses were calculated taking into account correlation within twin pairs. Analyses were computed with SAS, release 6.12 and STATA, release 6.

FINNISH TWIN COHORT - PAPER V

Study population
In 1975 a baseline questionnaire was administered to all twins of the Finnish Twin Cohort with an overall response rate of 89 percent. The first follow-up questionnaire was mailed in 1981 with a response rate of 84% and the second in 1990 with a response rate of 77%60,61. All three questionnaires included questions on lifestyle factors such as alcohol intake, smoking and physical activity, along with questions on psychosocial and medical conditions and questions for classification of zygosity. The present study consisted of 11,501 twin pairs (7,242 dizygotic pairs, 3,402 monozygotic pairs and 857 of unknown zygosity), free of diabetes at baseline.

Classification of exposure
Intake of alcohol was measured with separate questions on quantity of beer, wine and spirits used during an average week or month. Quantity was measured on three 7-point scales, with the upper limits defined as consuming ≥48 bottles of beer per week, ≥10 bottles of wine per week or ≥20 bottles of spirits per month. For each type of beverage, the reported consumption was converted into grams of absolute alcohol and summed to yield an estimate of total alcohol consumption in grams per day. To assess binge drinking, subjects were asked if they had consumed more than 5 bottles of beer, one bottle of wine or 4 drinks (≥18 cl spirits) on the same occasion at least once a month during the preceding year. In addition, the questionnaire in 1981 included a question on pass-outs due to alcohol consumption during the preceding year measured on a 5-point scale with more than seven times as the highest category.
Self-reported weight and height were used to calculate body mass index (BMI) as the square of height in meters divided by weight. Zygosity (monozygotic, dizygotic, unclassified) was classified on the basis of questions about strangers confusing the twins in childhood and similarity in childhood, a method that has been shown to be highly accurate in a validation study using genetic markers.68

Classification of diabetes
Incident cases of type 2 diabetes during the period 1972-1995 were identified through record linkage using information from the Finnish National Hospital Discharge Register together with information from a national drug register in Finland using the procedures described by Kaprio et al.69 In Finland, patients with diabetes are provided with anti-diabetic drug therapy fully or nearly free of charge. The prerequisite for such free medication is a patient application, based on a detailed medical certificate, which is kept in a national registry at the Social Insurance Institution. This registry is virtually complete with regard to type 1 diabetes but not with regard to type 2 diabetes because a large number of these patients are treated with diet only, at least for some time after diagnosis. The hospital register covers all hospital discharges in Finland since 1968 with diagnoses coded according to the international classification of disease (ICD 8 and ICD 9). All patients with a diagnosis code 250 (diabetes mellitus) were selected from the registry. These two registries were linked with the Twin Cohort using a unique personal identification number assigned to each Finnish citizen.

In order to determine type of diabetes, copies of original records from the two registers were reviewed. Copies of death certificates for the deceased were also examined. The classification was based on WHO criteria from 1985.75 Patients with an abrupt onset of the disease that required insulin from the time of diagnosis were classified as having type 1 diabetes. Those patients who only received oral medication or dietary therapy were classified as having type 2 diabetes and so were subjects in whom insulin therapy had been implemented as an adjuvant treatment to hypoglycaemic drugs. In all, 807 cases of diabetes were identified 1976-95, and for them information from the medical registries for classification of type of diabetes were obtained for 701 cases (87 percent). Based on review of these records 589 cases of type 2 diabetes were identified, 35 cases of type 1 diabetes, 38 cases of gestational diabetes, 19 cases of secondary diabetes, 5 cases were unclassifiable or other types. In addition, a history of diabetes was also asked for in all three questionnaires mailed to the Finnish Twin Cohort. We excluded subjects with diabetes at baseline either
based on register information or according to the 1975 questionnaire from the analyses (n=417). In addition we excluded subjects stating they had developed diabetes during the follow-up period but who were not identified through the registers (n=168).

**Data analyses**

Person years of follow up were accumulated starting January 1st, 1976. The follow-up was terminated at the date of diagnosis of diabetes, the date of death, the date of emigration from Finland or December 31st 1995, whichever came first. To analyse the association between alcohol consumption and type 2 diabetes we calculated relative risk estimates together with 95% confidence intervals using Cox proportional hazards models (SAS PHREG) adjusted for age and body mass index. Time-dependent analyses were performed using baseline information on alcohol together with information from 1981 and 1990, allowing subjects to change exposure category over time. Correspondingly, information on body mass index was updated during follow-up. To investigate the association between alcohol consumption and type 2 diabetes taking hereditary and childhood factors into account we calculated odds ratios (ORs) of type 2 diabetes in alcohol discordant twin pairs.
RESULTS

STOCKHOLM DIABETES PREVENTION PROGRAM

Paper 1- Weight history
The odds ratio of impaired glucose tolerance and diabetes increased with level of current obesity, both when obesity was defined by body mass index and by waist-hip ratio (Table 2). For impaired glucose tolerance, these analyses were split on family history of diabetes. The association with obesity was consistently more pronounced in subjects without family history of diabetes.

The prevalence of diabetes and impaired glucose tolerance increased with duration of obesity (Table 2). The odds ratios of diabetes increased from 1.9 among men with overweight during 0-4 years to 7.3 among men with overweight during 10 years or more.

Insulin resistance in subjects with impaired glucose tolerance was also investigated in relation to weight history. We found that the prevalence of relative insulin resistance, as estimated from fasting insulin levels, increased with longer duration of obesity. Hence, in men with duration of obesity of 10 years or longer the odds ratio was 21.0 (95% CI=2.1-206.4). The corresponding odds ratio in men with a short duration (<5 years) was 6.9 (95% CI=0.6-74.2). Similar results were obtained when insulin resistance was assessed by HOMA methodology.

The odds ratio for a low 2h-insulin response in subjects with impaired glucose tolerance, as estimated from 120-minute increase in insulin, was not increased in subjects with a short duration of obesity (OR=0.7, 95% CI=0.2-2.9). In subjects with a long duration of obesity, however, the odds ratio was 3.3 (95% CI=1.2-8.9). HOMA-assessment of β-cell function yielded similar, but slightly lower estimates.
Table 2. Odds ratio (OR) of impaired glucose tolerance and type 2 diabetes associated with obesity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Impaired glucose tolerance</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No family history of diabetes</td>
<td>Family history of diabetes</td>
</tr>
<tr>
<td></td>
<td>No. of normal/impaired glucose tolerance</td>
<td>OR</td>
</tr>
<tr>
<td>Present body mass index (kg/m²) *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>662/6</td>
<td>1.0</td>
</tr>
<tr>
<td>25.0-27.9</td>
<td>490/20</td>
<td>4.4</td>
</tr>
<tr>
<td>≥28.0</td>
<td>281/34</td>
<td>12.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.89</td>
<td>518/7</td>
<td>1.0</td>
</tr>
<tr>
<td>0.89-0.92</td>
<td>543/16</td>
<td>1.3</td>
</tr>
<tr>
<td>≥0.93</td>
<td>369/37</td>
<td>2.8</td>
</tr>
<tr>
<td>Duration of body mass index ≥25.0 kg/m² ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt;25.0</td>
<td>619/6</td>
<td>1.0</td>
</tr>
<tr>
<td>0-4 years</td>
<td>205/2</td>
<td>1.3</td>
</tr>
<tr>
<td>5-9 years</td>
<td>173/10</td>
<td>7.6</td>
</tr>
<tr>
<td>≥10 years</td>
<td>383/40</td>
<td>11.8</td>
</tr>
</tbody>
</table>

* Adjusted for physical activity (high, low) and age (35-40, 41-45, 46-51 and 52-56 years).
† Adjusted for physical activity, age and present body mass index (<25.0, 25.0-27.9, 28.0-29.9 and ≥30.0 kg m²).
‡ Adjusted for physical activity, age and present weight (<75.0, 75.0-79.9, 80.0-89.9 and ≥90.0 kg).
Paper II - Low birth weight

Subjects with low birth weight (≤3000g) had a higher prevalence of impaired glucose tolerance, impaired fasting glucose and diabetes compared to subjects with high birth weight (>3600g). The estimated odds ratios were 1.9 (95% CI=1.0-3.4), 2.6 (95% CI=1.3-4.9) and 4.5 (95% CI=1.9-10.8), respectively. When these analyses were performed by family history of diabetes a tendency for an increased odds ratio of impaired fasting glucose, impaired glucose tolerance and diabetes was found in men without diabetes in the family as in subjects with family history of diabetes (Table 3). The combination of low birth weight and family history of diabetes in relation to the prevalence of diabetes was also investigated. Subjects with low birth weight and family history of diabetes had an odds ratio of 10.9 (95% CI=2.9-41.2) compared to subjects with high birth weight and no family history.

Table 3. Odds ratio (OR) of glucose intolerance associated with low birth weight by family history of diabetes.

<table>
<thead>
<tr>
<th>Family history</th>
<th>Birth weight (g)</th>
<th>Impaired fasting glucose</th>
<th>Impaired glucose tolerance</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3601</td>
<td>17 1.0 1.0</td>
<td>25 1.0 1.0</td>
<td>7 1.0 1.0</td>
<td></td>
</tr>
<tr>
<td>3001-3600</td>
<td>14 1.0 0.5-2.0</td>
<td>33 1.8 1.0-3.2</td>
<td>11 2.0 0.8-5.3</td>
<td></td>
</tr>
<tr>
<td>≤3000</td>
<td>11 2.3 1.0-4.9</td>
<td>11 1.9 0.9-4.1</td>
<td>10 5.4 2.0-14.9</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3601</td>
<td>6 1.0 1.0</td>
<td>15 1.0 1.0</td>
<td>3 1.0 1.0</td>
<td></td>
</tr>
<tr>
<td>3001-3600</td>
<td>3 0.5 0.1-2.0</td>
<td>10 0.6 0.3-1.4</td>
<td>2 0.6 0.1-3.8</td>
<td></td>
</tr>
<tr>
<td>≤3000</td>
<td>6 3.3 1.0-10.4</td>
<td>8 1.8 0.7-4.3</td>
<td>2 2.3 0.4-14.4</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age (35-45, 46-56 years) and body mass index (<25.0, 25.0-27.9, 28.0-29.9 and ≥30.0 kg/m²).
† Adjusted for age (35-41, 42-48 and 49-56 years) and body mass index (<25.0, 25.0-27.9, 28.0-29.9 and ≥30.0 kg/m²).

Paper III - Alcohol consumption and prevalence of type 2 diabetes

Men reporting comparatively high alcohol consumption (highest quartile corresponding to 12 drinks per week or more) were more likely to have diabetes than subjects reporting low consumption (Table 4). In low and moderate consumers there were few cases and no definite difference in prevalence from occasional drinkers could be seen. For impaired glucose tolerance, a reduced prevalence was found at all three levels of regular alcohol consumption compared to occasional drinkers.
Table 4. Odds ratio (OR) of impaired glucose tolerance and type 2 diabetes associated with alcohol consumption. Stockholm Diabetes Prevention Program.

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Normal glucose tolerance</th>
<th>Impaired glucose tolerance</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
</tr>
<tr>
<td>Occasional</td>
<td>663</td>
<td>52 1.0</td>
<td>10 1.0</td>
</tr>
<tr>
<td>Low</td>
<td>683</td>
<td>29 0.6 0.3-0.9</td>
<td>7 0.7 0.3-1.8</td>
</tr>
<tr>
<td>Moderate</td>
<td>685</td>
<td>35 0.6 0.4-1.0</td>
<td>8 0.7 0.3-1.8</td>
</tr>
<tr>
<td>Heavy</td>
<td>649</td>
<td>42 0.7 0.5-1.1</td>
<td>25 2.1 1.0-4.5</td>
</tr>
</tbody>
</table>

Odds ratios and 95% confidence intervals (CI) are adjusted for body mass index (BMI), age (35-40, 41-46, 47-51 and 52-56 years), smoking (never, former and current), physical activity (high and low) and family history of diabetes (yes or no).

In subjects with family history of diabetes the odds ratio associated with high alcohol consumption was 3.1, 95% CI=1.3-7.4 for diabetes and 0.7, 95% CI=0.4-1.2, for impaired glucose tolerance. Corresponding estimates for moderate consumption were 0.8, 95% CI=0.2-2.3 (diabetes) and 0.5, 95% CI=0.3-0.9 (impaired glucose tolerance). In subjects without family history of diabetes, the odds ratio of impaired glucose tolerance was 0.8 (0.4-1.8) in high consumers and 1.0 (95% CI= 0.4-2.1) in moderate consumers. Corresponding estimates were not obtained for diabetes due to small numbers.

Separate analyses for type of beverage indicated that high consumers of beer, spirits and wine had an odds ratio for diabetes of 2.9 (95% CI=1.2-6.9), 3.3 (95% CI=1.4-7.8) and 1.2 (95% CI=0.5-2.7), respectively compared to low consumers of beer, wine and spirits.

FINNISH TWIN COHORT

Paper IV- Questionnaire information on alcohol consumption
Mean levels of CDT, gamma-GT and MCV showed a progressive rise with increased self-reported alcohol consumption already at low levels of reported consumption and there was a positive correlation between alcohol in grams consumed per day and levels of CDT, gamma-GT and MCV of 0.46, 0.32 and 0.36, respectively. The correspondence between questionnaire and interview information on alcohol consumption was fairly good.
(kappa=0.64) but overall, the estimated mean consumption of alcohol was 23 percent higher according to the interview than according to the questionnaire. Also, while the interview classified 34 (22%) subjects as high alcohol consumers the corresponding number was only 21 (14%) according to the questionnaire.

Table 5 displays the sensitivity and specificity of the questionnaire for identification of high consumers (≥30 g alcohol per day) using the interview and the biochemical indicators as reference methods. These analyses indicated sensitivity of about 40% and specificity of about 90%. We also combined information on grams of alcohol consumed per day (≥30 grams) with information on heavy drinking at one occasion and included moderate consumers (20-29.9 grams of alcohol per day) with binge drinking habits in the high consumption group. In a similar way we used information on drinking problems and included subjects who reported moderate consumption and current or previous drinking problems in the high consumption group. By doing this, sensitivity was almost twice as high while specificity remained high, compared to when we only used information on amount consumed.

Table 5. Sensitivity and specificity of self-reported questionnaire data for identification of high alcohol consumers using information from a diet history interview and biochemical markers (CDT, gamma-GT and MCV) as reference methods.

<table>
<thead>
<tr>
<th>Reference method</th>
<th>High alcohol intake ≥30 g/day</th>
<th>High alcohol intake ≥30 g/day or ≥20 g/day and binge drinking</th>
<th>High alcohol intake ≥30 g/day or ≥20 g/day and previous drinking problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interview (≥30g/day)</td>
<td>41%</td>
<td>94%</td>
<td>82%</td>
</tr>
<tr>
<td>CDT (≥6.0 %)</td>
<td>40%</td>
<td>89%</td>
<td>73%</td>
</tr>
<tr>
<td>Gamma-GT (≥80.0 U/L)</td>
<td>28%</td>
<td>89%</td>
<td>44%</td>
</tr>
<tr>
<td>MCV (≥96.0 fl)</td>
<td>43%</td>
<td>88%</td>
<td>67%</td>
</tr>
</tbody>
</table>

Paper V- Alcohol consumption and incidence of type 2 diabetes.
High alcohol consumption (≥50 g alcohol per day) was not associated with an increased risk of diabetes in men (RR=1.0, 95% CI=0.6-1.9). There was however a tendency for an increased risk in women (RR=1.6, 95% CI=0.8-3.5), reporting consumption of 20 grams of
alcohol per day or more. Classifying moderate consumers with binge drinking habits into the highest consumption group had only minor effect on the relative risk associated with high alcohol consumption: RR= 0.8, 95% CI=0.6-1.2 (men) and RR= 1.3, 95% CI=0.7-2.5 (women). Moderate alcohol consumption (15-29.9 g/day in men, 5-9.9 g/day in women) was associated with a relative risk of 0.7 (95% CI=0.5-1.1) in men and 0.7 (95% CI=0.4-1.3) in women. Analyses of alcohol discordant twin pairs suggested a reduced odds ratio (OR=0.5, 95% CI=0.2-1.3) of type 2 diabetes in moderate consumers of alcohol (15-29.9 g/day) compared to their low-consuming (<5 g/day) siblings.

When the analyses were stratified by overweight at baseline, moderate consumption was associated with a reduced incidence of type 2 diabetes in overweight, but not in lean and normal weight subjects (Table 6). Also, in lean and normal weight women a comparatively high consumption was associated with an increased incidence of type 2 diabetes.

Table 6. Relative risk of type 2 diabetes associated with alcohol consumption by body mass index. Finnish Twin Cohort 1976-95.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25.0</td>
<td>≥25.0</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cases</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Abstainer</td>
<td>14</td>
<td>1.9</td>
</tr>
<tr>
<td>Low</td>
<td>17</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>22</td>
<td>1.3</td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Relative risks and 95% confidence intervals (CI) are adjusted for age and body mass index. Alcohol information from 1975, updated in 1981 and 1990. Numbers of cases are from distribution in 1975. Low alcohol consumption: 5 g alcohol/day; moderate: 5-29.9 g in men, 5-19.9 g in women; high: ≥30.0 g/day in men, ≥20.0 g/day in women.

Binge drinking was not associated with type 2 diabetes in men (RR=0.9, 95% CI=0.6-1.3). Women reporting binge drinking or passing out due to alcohol consumption had an increased incidence of type 2 diabetes (RR=2.1, 95% CI=1.0-4.4) and RR=2.4, 95% CI=1.1-5.0, respectively).
DISCUSSION

RESULTS

Weight history
The results from this thesis support previous findings indicating that duration of obesity as well as degree of obesity increases the risk of glucose intolerance. Our results confirm that insulin resistance increases with degree of obesity but also suggest that insulin resistance increases in a similar way with duration of obesity. In addition, long duration of obesity was associated with low insulin secretion, whereas no association was seen with short duration. These findings indicate that obesity primarily affects insulin resistance, with no or a short latency period whereas when obesity is prolonged, there is also an inhibitory effect on insulin secretion. These findings support the hypothesis that obesity, through insulin resistance, increases the demand for insulin and that the increased demand eventually results in decreased insulin secretion due to β-cell exhaustion.

Several studies have shown that the association between obesity and glucose intolerance is more pronounced in subjects without family history of diabetes than in subjects with diabetes in the family. It has been argued that this reflects that a greater amount of obesity is required to result in diabetes in subjects without a genetic predisposition for the disease. In our study, analyses with odds ratios indicated that the association between obesity and glucose intolerance was more pronounced in subjects without family history of diabetes. However, absolute analyses demonstrated the opposite, that the association was more pronounced in men with diabetes in the family. In our study, the interpretation thus depends on whether relative or absolute measures of the association were employed.

Low birth weight
The association between low birth weight and family history of diabetes has been attributed primarily to environmental factors such as fetal malnutrition. It is also possible that genetic factors that predispose for diabetes could include a propensity for low birth weight. In this thesis, adjustment for family history of diabetes had very little impact on the association between low birth weight and glucose intolerance, which is in agreement with the results of two previous studies. Furthermore, the results indicated that the association was present in subjects with as well as without diabetes in the family. Altogether, these results support the hypothesis that the association between low birth weight and diabetes, at least in part, is due to environmental factors. However, the prevalence of diabetes was particularly high in men with both low birth weight and diabetes in the family. This indicates that low birth weight
may be of greater importance for the development of diabetes among subjects with family history of the disease. The results should be interpreted with caution as the analyses were based on very small numbers in men without diabetes in the family.

**Alcohol consumption**
We investigated the relationship between alcohol and type 2 diabetes in the Stockholm Diabetes Prevention Program: a comparatively small, cross-sectional study with diabetes diagnosed by screening, and in the Finnish Twin Cohort: a large, prospective study where diabetes was identified by record linkage. Both studies are compatible with a protective effect of moderate alcohol consumption on the risk of diabetes as indicated by others\(^\text{24-32}\). A reduced prevalence of impaired glucose tolerance was also seen in moderate consumers, which was reported by Hodge et al\(^\text{36}\). In addition, the results based on the Finnish study suggested that the protective effect of alcohol primarily concerns overweight subjects. This seems biologically plausible as alcohol intake may increase insulin sensitivity\(^\text{38-39}\) and thus counteract obesity-induced insulin resistance.

With regard to high alcohol consumption the results differed between Stockholm Diabetes Prevention Program and the Finnish Twin Cohort. In the Stockholm study, the prevalence of diabetes was increased in high compared to low consumers of alcohol. There was no corresponding increase in the Finnish study although there was a similar tendency in high consuming women. Also, in women but not in men of the Finnish Cohort, binge drinking was associated with an increased risk of diabetes. This is to our knowledge the first study to suggest that alcohol consumption may increase the risk of diabetes in women.

The discrepant results on the relationship between high alcohol intake and diabetes in the literature and in our two studies could at least in part be due to differences in methodology. Consumption levels were higher overall in the Finnish study. Therefore higher cut-off levels where used to categorize subjects in that study compared to the Stockholm study. Still, recalculating the data from the Stockholm study using the same cut-off levels as in the Finnish study did not change the results markedly. Notably, all studies indicating an increased risk in high consumers, including the Stockholm study, have investigated diabetes diagnosed by screening\(^\text{24-27, 31-34}\) whereas the studies using self-reports or as in the Finnish study, register data all indicate a lack of association or a protective effect of high alcohol consumption\(^\text{28-32}\). Screening will detect mild forms of diabetes without symptoms that will be missed in studies based on self-reports or register data thus introducing misclassification in those studies. Even if sensitivity for identification of cases is low, the relative risk will not be
affected as long as sensitivity is not related to exposure. However, alcohol consumption may be related to medical or socio-economic factors that influence the frequency of medical contacts and hence the likelihood of being diagnosed with diabetes. If so, the risk estimates in studies based on self-reports or register data may be biased. It seems as if the most probable consequence of such differential misclassification would be under-diagnosing in high consumers which would lead to an underestimation of the relative risk associated with high alcohol consumption. Another explanation for the different results in studies based on screening versus studies based on known diabetes cases could be that high alcohol intake primarily promotes mild forms of type 2 diabetes.

Misclassification of alcohol consumption may contribute to dilute the association between high alcohol intake and type 2 diabetes. We compared information on alcohol from a questionnaire, similar to the one used for the Finnish Twin cohort, to interview information on alcohol and information from three biochemical indicators of alcohol intake. This comparison suggested that only about 40 percent of subjects with high alcohol consumption according to the interview or to the biochemical markers, would be identified by the questionnaire. On the other hand, specificity was high implying that few subjects would erroneously be classified as high consumers by the questionnaire. A substantial proportion of the high consumers thus seems to be misclassified into lower consumption categories. In studies of alcohol and disease, such as diabetes, this misclassification would tend to dilute the relative risk in high consumers. Furthermore, in moderate consumers the risk estimate could be biased either towards an over or underestimation. The effect of this misclassification can be illustrated in a numerical example: We hypothesize a situation where high consumers of alcohol have a relative risk of 2 for some disease and furthermore, that 10% of the subjects are exposed, i.e. high consumers. In this situation, given a true relative risk of 2 and using a questionnaire with 40% sensitivity and 90% specificity for identification of high consumers, we would observe a relative risk of 1.3. The ability of the questionnaire to identify high consumers could be improved by supplementing information on amount consumed with information on binge drinking habits or previous drinking problems.

We tried to improve our classification of high alcohol consumers in the Finnish Twin Cohort by the use of both information on amount consumed and information on binge drinking habits. With this refined classification there was still no association between high alcohol intake and diabetes.
METHODOLOGY

Study design
In epidemiological studies of associations between exposure and disease it is generally preferable to base the analyses on estimates of incidence in the groups compared. Three of the studies of this thesis were based on a cross-sectional study. The analyses were thus performed on prevalent cases of diabetes. Prevalence of a disease is influenced not only by incidence but also by duration of the disease. Furthermore, the time sequence between exposure and disease is often not obvious in a cross-sectional study. As a result, causal interpretations of the observed associations are hampered. The cross-sectional design is most likely of less importance for causal interpretations in analyses of birth weight than of obesity or alcohol consumption in relation to type 2 diabetes. The relevance of the cross-sectional results also depends on the correlation between reported exposure and exposure from the period before onset of the disease. Still, the mild form of diabetes we investigated and the fact that subjects were unaware of the disease makes it less likely that changes in lifestyle, such as alcohol consumption would occur as a result of disease onset.

Misclassification of disease
In the Stockholm Diabetes Prevention Program we identified cases of diabetes by screening, thereby avoiding the under-diagnosing that would have been inevitable if only known cases of diabetes had been used. Such under-diagnosing can be substantial; a previous Swedish study indicated that the proportion of cases of undiagnosed diabetes is about 50% of the frequency of known diabetes. However, in order to avoid an influence of knowledge of and treatment for diabetes on the associations investigated in this thesis, all subjects with known diabetes at baseline were excluded. This means that cases basically had mild forms of diabetes, essentially without symptoms. It is not entirely clear to what extent the results can be extrapolated to more severe forms of diabetes. Although there is no definite evidence that the aetiology of type 2 diabetes is different in mild compared to more severe forms of the disease this remains a possibility. There was some information on potential risk factors such as weight and birth weight for those with known diabetes who were excluded from the study. Notably, the relative risk associated with low birth weight was less pronounced for manifest diabetes. However, the exposure information of those with known diabetes may be less reliable as knowing about their diabetes may have introduced recall bias.

The cases of the Finnish Twin Cohort were subjects with already diagnosed diabetes who had received either medication for their diabetes or been hospital treated. The method of case identification has been shown to detect 80% of known cases of diabetes in a population. Those with mild forms of the disease treated only by diet and not requiring hospital care will be missed in addition to those with unknown diabetes. As long as misclassification is not
related to exposure, a crude method for identification of cases will not result in a spurious association. However, as discussed above, alcohol consumption may be related to the likelihood of being hospital treated or of being medicated for your diabetes and if so, this methodology may have introduced differential misclassification of cases.

A related issue is the type of diabetes that we investigated. In the Stockholm study, the age span investigated (35-56 years) makes it likely that most subjects in whom we diagnosed hyperglycemia had type 2 diabetes and not type 1 diabetes. This was also supported by a clinical follow-up of subjects diagnosed with diabetes: all subjects had mild diabetes and none needed insulin treatment during the observation time of at least one year. In the Finnish study, type of diabetes was assessed by careful review of records over medication and symptoms at onset.

In order to shed light on possible mechanisms underlying the observed associations we investigated insulin resistance and secretion in relation to our exposures of interest. In subjects with manifest diabetes, estimating insulin resistance and secretion is difficult as hyperglycemia itself alters these conditions\textsuperscript{76}. Instead we have investigated parameters reflecting insulin resistance and secretion in men with impaired glucose tolerance, i.e. a state in which metabolic abnormalities associated with diabetes were minimized. It should be noted that our measures reflecting insulin resistance and secretion were crude. Nevertheless, high fasting insulin concentrations are widely used as indicators of insulin resistance and are known to correlate well with more sophisticated measures such as euglycemic clamp technique\textsuperscript{77-79}. Using low 2h-insulin response as a measure of insulin secretion is more controversial. In subjects with normal glucose tolerance low 2h insulin response can reflect the return to fasting glucose levels rather than the existence of an impaired insulin response. However, in subjects with impaired glucose tolerance, low 2-h insulin response has been shown to be an indicator of later development of type 2 diabetes\textsuperscript{79-82}. With regard to the HOMA methodology used for defining insulin resistance and \(\beta\)-cell function, others have validated it against the hyperglycemic clamp method and euglycemic hyperinsulinemic clamp technique with high agreement\textsuperscript{87}.

**Misclassification of exposure**
The use of self-reported questionnaire information for the main exposures may have introduced a bias in our results, due to misclassification. Self-reported information on birth weight and weight has previously been validated against medical records with good agreement\textsuperscript{74,83-85}. With regard to weight, individuals with overweight have been shown to underestimate their previous weight whereas subjects of low weight often overestimate their
weight\textsuperscript{16} Still, such misclassification would tend to result in underestimates of the relationship between obesity and glucose tolerance and is unlikely to explain the increased prevalence of diabetes that we observed among subjects with obesity. The self-reported information on alcohol consumption used in paper III and V is perhaps most problematic and a separate study was performed to investigate the quality of this information. As mentioned above our results in paper IV suggest that underreporting will lead to substantial misclassification of high consumers of alcohol. In general, non-differential misclassification will tend to bias the risk estimate for the highest exposure category towards 1.0 and distort dose-response relationships. Thus, it does not seem likely that the increased prevalence in high consumers demonstrated in paper III is explained by misclassification of alcohol intake. A definite advantage in the Swedish cross-sectional study was that subjects were unaware of disease status when answering the questionnaire thus making differential misclassification of alcohol intake as well as previous weight or birth weight less likely. In the Finnish study, misclassification of alcohol intake can be assumed to be non-differential as this was a prospective study with exposure information collected before disease onset. Still, the known underestimation of alcohol intake in self-reported data means that the estimated grams of consumed alcohol per day used for categorization of subjects in categories of low, medium or high consumption should not be interpreted as an estimated of the absolute actual consumption\textsuperscript{16}

\textbf{Selection}
In the Stockholm study the sample was restricted to men born in Sweden who had either strong family history of diabetes or no close relatives with diabetes. Hence, men with foreign origin or insufficient family history of diabetes according to our inclusion criteria were excluded. The reason for the inclusion and exclusion criteria was essentially to enrich the study sample with regard to family history of diabetes in an ethnically relatively homogenous population. In the first stage of the investigation the participation rate was about 80% and in the second stage about 70%, which must be regarded as reasonable, particularly considering that the health examination was so extensive. Still, it is possible that the non-response has influenced our results. Record linkage to information from the 1990 census revealed that the participants on average were better educated, had higher socio-economic status and income than the source population. We consider it unlikely that non-response can explain our main findings since it seems reasonable to assume that participation was unrelated to disease status within the different exposure categories. This assumption is based on the fact that the cases in our study consisted of men with previously unknown diabetes, basically without symptoms. In other words, even if overweight subjects are underrepresented in our study, we have no reason to believe that overweight subjects with and without diabetes differ in this respect. Hence, the loss of overweight subjects will not result in a spurious association between
obesity and type 2 diabetes. It seems particularly important to consider the non-responders with regard to our study on alcohol and diabetes. Although we do not have the information to confirm this, it is plausible that some groups of the source population were underrepresented with regard to alcohol consumption, e.g. subjects with alcohol abuse. Therefore, it cannot be ruled out that the association with diabetes and impaired glucose tolerance for the high alcohol consumption category would have been somewhat different, probably stronger, if these subjects had been included. Furthermore, consumption levels would probably have been higher.

Paper II was based on fewer subjects than the other studies based on Stockholm Diabetes Prevention Program, as about 30% of the respondents did not know their birth weight. The important question arises as to whether subjects that do not know their birth weight differ from subjects who do. It seems possible that many of the non-responders belonged to the middle birth weight category since subjects with a more extreme birth weight, high or low, may be more likely to know their birth weight. We see no reason however, why subjects with impaired glucose tolerance or diabetes would differ from healthy subjects with regard to knowledge about birth weight. It should also be noted that the non-response rate was similar in men with normal glucose tolerance and impaired glucose tolerance or diabetes. However, in part owing to the non-responses, small numbers hampered the analyses of birth weight, particularly in subjects without diabetes in the family.

The response rate of the Finnish Twin Cohort was generally high in the baseline questionnaire as well as in the follow-up investigations. Still, as mentioned above, non-response may be related to high alcohol consumption and the reported relationship between alcohol consumption and type 2 diabetes in paper V might have been different if we could have investigated the whole study population. During the follow-up, emigration and mortality was monitored in the Cohort. This was done by record linkage to the Finnish national mortality register and the national population registers using the personal identification number assigned to each Finnish citizen. These registers have a high completeness and the population registers are frequently updated with information on vital status and changes in residence. Thus, it does not seem likely that our main results in paper V were strongly influenced by loss of subjects during follow-up.

Confounding
A strength in the studies of the present thesis was that we were in general able to take many potential confounders into account, including family history of diabetes. Some considerations
concerning confounding should be mentioned. Family history of diabetes is probably not only an indicator of heredity but also of family-shared conditions, such as social class, family values, educational levels and eating habits. Furthermore, in paper I we adjusted for degree of obesity when investigating duration of obesity by including current weight in the analyses. Since duration and degree of obesity are so closely correlated, adjusting for one of them when investigating the other may be futile. Hence, whether duration of obesity increases the risk of diabetes by way of increasing levels of obesity remains a possible explanation behind the observed association with duration of obesity. Furthermore, in paper II on birth weight, the results are limited owing to the fact that no information on factors such as size at birth, gestational age and smoking in the mother was available. Finally, confounding is a particular problem in studies on alcohol, since alcohol consumption is known to be closely related to several other lifestyle factors that may be associated with an increased risk of diabetes. Adjustment for overweight, smoking, physical activity and socio-economic group did not account for the observed association between alcohol and type 2 diabetes. However, dietary factors may also affect the risk of type 2 diabetes as well as be related to alcohol consumption. Unfortunately, only limited information on dietary factors was available why we were not able to take diet into account.

CONCLUSIONS

The results of this thesis suggest that duration of obesity is an important risk factor for type 2 diabetes in addition to degree and distribution of obesity. When our study was published in 1998, few studies had investigated this issue but the importance of duration of obesity has since then been confirmed in additional studies. This finding emphasizes the important role of obesity in the aetiology of type 2 diabetes and the need to reduce overweight, preferably at an early stage, in order to reduce incidence of the disease.

The association between low birth weight and type 2 diabetes has been attributed to environmental factors, primarily long-term effects of fetal malnutrition. It has also been suggested that low birth weight may only be a marker for genetic factors influencing fetal growth as well as risk of type 2 diabetes. The study design of the Stockholm diabetes prevention program provided a unique opportunity to study to what extent confounding from family history of diabetes may influence the association between low birth weight and type 2 diabetes. The results indicate that the association between low birth weight and diabetes persists even after adjustment for family history of diabetes. These findings support that factors related to intra-uterine environment could be of importance for the development of
type 2 diabetes. To what extent the association between low birth weight and adult disease reflects environmental or genetic factors is, however, still a matter of controversy.

The results of this thesis add to the accumulating evidence suggesting that moderate alcohol consumption reduces the risk of type 2 diabetes. Our results suggested that this reduced risk primarily concerns overweight subjects. This finding is compatible with previous findings indicating that alcohol may enhance insulin sensitivity. Future studies on the relationship between alcohol consumption and type 2 diabetes are warranted to assess the shape of the association between alcohol consumption and type 2 diabetes over the range from abstention to high consumption and in particular to analyse to what extent high alcohol consumption may increase the risk of diabetes. The possible protective effect of moderate alcohol consumption also needs further attention, considering influence from overweight and type of beverage. In design and interpretation of future studies on alcohol consumption and type 2 diabetes it is important to consider the accuracy of self-reported information on alcohol consumption.
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