Weight History, Glucose Intolerance, and Insulin Levels in Middle-aged Swedish Men

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The association between weight history and glucose intolerance was examined in a cross-sectional study consisting of 3,128 Swedish men aged 35-56 years, 52 percent of whom had a family background of diabetes mellitus. Oral glucose tolerance testing detected 55 cases of type 2 (non-insulin-dependent) diabetes and 172 cases of impaired glucose tolerance. Among men with no family history of diabetes, the estimated odds ratios for impaired glucose tolerance associated with short (<5 years) and long (≥10 years) durations of obesity (body mass index (weight (kg)/height(m)^2) ≥25.0) were 1.3 (95% confidence interval (CI) 0.2-7.7) and 11.8 (95% CI 3.3-41.9), respectively. Among men with a family history of diabetes, the odds ratios were 2.0 (95% CI 0.8-4.7) and 4.0 (95% CI 1.8-9.1), respectively. Corresponding estimates of the odds of type 2 diabetes, adjusted for family history of diabetes, were 1.9 (95% CI 0.5-7.1) and 7.3 (95% CI 2.2-23.7), respectively. The odds of high (≥30.0 μU/liter) fasting insulin levels in subjects with impaired glucose tolerance were 6.9 (95% CI 0.6-74.2) and 21.0 (95% CI 2.1-206.4) for short and long durations of obesity, respectively. Corresponding estimated odds of low 2-hour insulin response (≤71.9 μU/liter) were 0.7 (95% CI 0.2-2.9) and 3.3 (95% CI 1.2-8.9). Homeostasis model assessment of insulin resistance yielded an odds ratio of 6.7 (95% CI 0.6-73.4) for a short duration of obesity and 20.0 (95% CI 2.0-200.6) for a long duration. Examination of β-cell function with homeostasis model assessment resulted in odds ratios of 0.2 (95% CI 0.0-1.6) and 2.0 (95% CI 0.7-5.4) for short and long durations of obesity, respectively. These data indicate that obesity decreases glucose tolerance by way of progressively increased insulin resistance and, in the case of prolonged duration, by decreased insulin secretion as well. Am J Epidemiol 1998; 148:539-45.

Obesity is the most recognized environmental risk factor for type 2 (non-insulin-dependent) diabetes mellitus. Numerous studies have shown that the risk of diabetes increases with the magnitude of obesity, following a dose-response relationship (1, 2). However, few studies have addressed the association between weight history and glucose intolerance (3, 4). As to mechanisms, overweight is known to affect glucose intolerance by way of insulin resistance (5). The mechanisms underlying the diabetogenic influence of obesity after a long duration may differ from those underlying the more immediate effects. Results from a study of Pima Indians indicated that a long duration of obesity was associated with low insulin response rather than with insulin resistance (4). However, to our knowledge, similar studies in Caucasians with less pronounced obesity are lacking. In addition, previous studies on weight history have been limited by the fact that family history of diabetes, another important risk factor (1), was not taken into account (3, 4).

The aim of the present study, the Stockholm Diabetes Prevention Programme, was to investigate the associations between weight history and the magnitude of glucose intolerance and parameters reflecting insulin resistance and insulin release. This population-based cross-sectional study was designed to account for family history of diabetes by enriching the sample in relation to family history of diabetes. Consequently, we have investigated a sample in which approximately

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50 percent of the subjects had a family history of diabetes instead of the 15–20 percent found in the general Swedish population.

MATERIALS AND METHODS

Study population

The baseline study of the Stockholm Diabetes Prevention Programme comprised men born between 1938 and 1957 and thus aged 35–56 years at the time of the examination (1992–1994). The study sample was drawn from four Swedish municipalities—Sigtuna, Tyresö, Upplands-Bro, and Värmdö—all situated on the outskirts of the city of Stockholm. The men were identified by means of the population registry kept by the Stockholm County Council.

The sample was obtained in two steps. First, all men of relevant age received a one-page postal questionnaire asking about country of birth and the presence of diabetes in their family as well as in themselves. Of 12,952 subjects, we obtained completed questionnaires from 10,236 (79 percent) after one or two reminders were sent by mail. Among those who responded, we identified 2,106 (20.6 percent) subjects with a 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 3,329 (32.5 percent) subjects without diabetes in their family; i.e., they had neither first- or second-degree relatives nor cousins with known diabetes. There were 1,531 (15.0 percent) men that did not fit the criteria for these two groups and 2,800 (27.4 percent) men who were unable to give complete answers regarding family history. These men were excluded, along with 258 (2.5 percent) persons who reported known diabetes and 212 (2.1 percent) persons who reported foreign origin (figure 1).

Secondly, all 2,106 men with a family history of diabetes, along with 2,424 subjects randomly selected within 5-year age groups among those without a family history of diabetes, were contacted by telephone and invited to undergo a physical examination at a primary health care center. In total, 3,162 (70 percent) persons agreed to participate. During the visit at the health care center, the information obtained from the postal questionnaire regarding family background of diabetes was confirmed by questioning the subject. As a result of this verification process, another 33 persons were excluded, along with 258 (2.5 percent) persons who reported known diabetes and 212 (2.1 percent) persons who reported foreign origin (figure 1).

Classification of glucose tolerance

At the health care center, the subjects underwent a standardized 75-g oral glucose tolerance test in the morning, after an overnight fast. Venous blood samples were taken before and 2 hours after glucose ingestion. Impaired glucose tolerance was defined according to World Health Organization criteria (6) as 2-hour plasma glucose levels of 7.8–11.0 mM, and diabetes was defined as 2-hour plasma glucose levels of ≥11.1 mM.

Classification of insulin resistance and secretion

Among men with impaired glucose tolerance, fasting insulin concentrations in the highest tertile (≥30.0 mU/liter) were defined as relative insulin resistance. Men with impaired glucose tolerance and a rise in insulin levels in the lowest tertile (<71.9 mU/liter) up to 120 minutes after glucose loading were defined as having relatively low insulin response. If a subject

![Diagram of study design](https://academic.oup.com/aje/article-abstract/148/6/539/106784/106784)
fitted the definitions for both the insulin resistance group and the low 2-hour insulin response group, he was not included in the analyses \((n = 7)\). In addition, we calculated insulin resistance and insulin secretion on the basis of the relation between fasting glucose levels and fasting insulin levels using the homeostasis model assessment (HOMA) method \((7)\). As suggested by Lithell et al. \((8)\), HOMA(\(\beta\)-cell function) was calculated as insulin/(glucose − 3.5) and HOMA(insulin resistance) was calculated as insulin \(\times\) glucose (equivalent to the original formulas, removing the constants 20 (\(\beta\)-cell function) and 22.5 (insulin resistance)). The highest tertile of the HOMA(resistance) parameter in subjects with impaired glucose tolerance was arbitrarily defined as relative insulin resistance (≥161.1). Men with impaired glucose tolerance and HOMA(\(\beta\)-cell function) values in the lowest tertile (≤11.2) were defined as having relatively low insulin secretion. Seven subjects with values in both the highest tertile of HOMA(resistance) and the lowest tertile of HOMA(\(\beta\)-cell function) were excluded from the analyses.

**Classification of exposure**

The health examination included measures of body height and weight. These measures were performed with the subject wearing light indoor clothing and no shoes. Waist and hip circumferences were assessed using a measuring tape with the subject lying down. The subject also filled out a questionnaire regarding information on previous weight and physical activity. In addition, the questionnaire included questions on birth weight, dietary habits, health status, alcohol and tobacco use, and psychosocial conditions.

Body mass index was calculated as the ratio of body weight (kg) to the square of height (m). Present body mass index was based on weight and height measurements made during the health examination, and body mass indices 5 and 10 years previously were based on self-reported information about previous weight obtained from the questionnaire, together with present height. Values for present body mass index were divided into three groups: ≤24.9, 25.0–27.9, and ≥28.0. We also analyzed body mass index as a continuous variable. We used present body mass index along with the information on body mass indices 5 and 10 years previously to compute duration of obesity. Subjects who had a body mass index greater than 24.9 10 years previously to compute duration of obesity. Subjects were divided into three groups: <24.9, 25.0-27.9, and >28.0.

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**Data analysis**

Estimated odds ratios and 95 percent confidence intervals were obtained by multiple logistic regression analysis. In all analyses, men with normal glucose tolerance were used as the comparison group. We adjusted for confounding by including the following variables in the logistic regression model. Physical activity (high/low) and age group (35–40, 41–46, 47–51, and 52–56 years) were included in all analyses. Additional adjustment was made for family history of diabetes (yes/no), present body mass index (≤24.9, 25.0–27.9, 28.0–29.9, and ≥30.0), and present weight in either three (≤77.9, 78.0–87.9, and ≥88.0 kg) or four (≤74.9, 75.0–79.9, 80.0–89.9, and ≥90.0 kg) groups (see footnotes to tables). The analyses were carried out with the SAS/STAT statistical package \((9)\).

**RESULTS**

We identified 172 (5.5 percent) men with impaired glucose tolerance and 55 (1.8 percent) men with type 2 diabetes.

**Glucose intolerance**

The prevalence of impaired glucose tolerance and diabetes increased consistently with increasing body mass index. Among men with no family history of diabetes, the odds ratios for impaired glucose tolerance associated with body mass indices of 25.0–27.9 and ≥28.0 were 4.4 and 12.5, respectively. Among men with a family history of diabetes, these estimates were 2.9 and 6.8. The increase in the odds ratio per 1-unit increase in body mass index was 27 percent.
among men with no family history of diabetes and 21 percent among men with diabetes in their family (table 1).

Among subjects with a family history of diabetes, the odds ratio for diabetes in those with a body mass index of 25.0–27.9 was 1.1, and in those with a body mass index of ≥28.0, it was 2.7. We were not able to conduct a corresponding analysis in men with no family history of diabetes, since only 10 of the 55 men with diabetes did not have a family history. As table 1 shows, the pooled estimates, adjusted for family history of diabetes, were slightly stronger than those for men with a family history of diabetes.

The odds ratio for impaired glucose tolerance in men with the highest waist:hip ratio was increased nearly threefold in comparison with men with the lowest waist:hip ratio. The results did not differ by subgroup of family history of diabetes (table 1). The increase in the odds ratio per 1 percent increase in waist:hip ratio was approximately 5 percent both in men with a family history of diabetes and in men without it. In men with a family history of diabetes, the odds ratio for diabetes associated with the highest waist:hip ratio versus the lowest was 5.7 (95 percent confidence interval (CI) 1.8–17.9), similar to that obtained in the pooled data after adjustment for family history (table 1).

The prevalence of impaired glucose tolerance increased with duration of overweight (table 1). In men with no family history of diabetes, the odds ratio for impaired glucose tolerance increased from 1.3 among men who were overweight for 0–4 years to approximately 12 among men who were overweight for 10 years or more. Corresponding results among men with a family history of diabetes were 2 and 4 (table 1). Among subjects with a family history of diabetes, the odds ratios for diabetes associated with durations of obesity of 0–4 years, 5–9 years, and ≥10 years were 1.9 (95 percent CI 0.5–7.6), 5.5 (95 percent CI 1.3–23.4), and 5.1 (95 percent CI 1.4–18.7), respectively. When pooled data were adjusted for family history of diabetes, these estimates ranged from 1.9 to 7.3 (table 1).

### Insulin resistance and response/secretion in subjects with impaired glucose tolerance

The prevalence of relative insulin resistance in subjects with impaired glucose tolerance, as estimated from high fasting insulin concentrations (≥30.0 mU/liter), increased with present body mass index and duration of obesity, following a dose-response relationship (table 2). The increase in the odds ratio was 37 percent for a 1-unit increase in body mass index. The odds ratio associated with duration of obesity increased from 6.9 in men with 0–4 years of obesity to 21.0 in men with 10 or more years of obesity. When insulin resistance was assessed with HOMA, the results were virtually the same (table 2).

The odds ratio for relatively low 2-hour insulin
response, based on 120-minute increase in insulin level, among subjects with impaired glucose tolerance was almost threefold higher for the highest category of body mass index (≥28.0) (table 2). A 1 percent increase in body mass index was associated with 13 percent increase in the odds ratio. A short duration (0–4 years) of obesity was not associated with an increased odds ratio for low insulin response, but the estimates were based on small numbers. However, a long (≥10 years) duration of obesity was associated with an odds ratio of 3.3. The corresponding estimates based on the HOMA algorithm of β-cell function were similar to but less pronounced than those based on the increase in insulin level over a period of 120 minutes (table 2).

### DISCUSSION

The cross-sectional design of this study does not allow us to rule out the possibility that glucose intolerance precedes obesity. However, it has been shown in several prospective studies that obesity precedes type 2 diabetes (10, 11). Furthermore, insulin resistance has been suggested to reduce further weight gain in Pima Indians (12), and the onset of manifest diabetes is known to be associated with weight loss. The implications of the latter two findings are that these odds ratios are probably underestimated to some extent. This might also explain why we found a weaker relation between present level of obesity and type 2 diabetes than between obesity and impaired glucose tolerance. However, the weaknesses of the cross-sectional study design must be borne in mind in interpreting these results, and future prospective studies must confirm the associations before they can be considered causal.

Another source of uncertainty is the type of diabetes present in the studied subjects. The lower age limit (35 years) makes it likely that most of the subjects in whom we diagnosed hyperglycemia had type 2 diabetes. Moreover, the findings can only be said to relate to milder forms of diabetes with symptoms that do not compel the affected subjects to seek medical treatment. A definite advantage of the study, however, is that the subjects were unaware of their disease status when answering the questionnaire; this is why recall bias is less likely.

The results of this study indicate that overweight decreases glucose tolerance and that this relation depends on duration as well as magnitude of obesity. We found that the association between glucose intolerance and duration of obesity follows a dose-response relationship. This confirms results from a previous study of type 2 diabetes in Pima Indians (4) but also extends those findings by showing a similar association with impaired glucose tolerance. In addition, we found a dose-response relationship between magnitude of present obesity and glucose intolerance that was seen regardless of whether obesity was measured as body mass index or as waist : hip ratio.

In consistency with some previous findings (13–15), we found that the odds ratio for glucose intolerance associated with obesity was stronger among men without diabetes in their family. This could reflect the fact that...
that the baseline occurrence of glucose intolerance is lower in normal weight (body mass index <25.0) persons without a family history of diabetes than in normal weight persons with a family history.

Information on duration of obesity was based on self-reported previous weights, which may have introduced potential bias. In one study (16) that compared self-reported information on previous weight with previously measured weight, 80 percent of the participants were able to estimate their weight of 10 years earlier within 7 kg (15 pounds). Subjects that were presently overweight tended to underestimate their previous weight, whereas subjects presently of low weight tended to overestimate their previous weight. Hence, in this particular study, it is more likely that subjects with glucose intolerance underestimated their previous weight, since this group had a higher mean body mass index than those with normal glucose tolerance. Rather than enhance the reported results, this would lead to dilution of the odds ratio estimates. Another problem is that subjects with a long duration of obesity are more obese than subjects with a short duration. To account for this, we adjusted for present weight in four categories in the analyses. The residual confounding remaining after this adjustment was probably not strong.

The presence of obesity is known to be diabetogenic by way of insulin resistance (2). Whether the effect of a long duration of obesity is mediated through insulin resistance and/or through effects on insulin secretion is largely unclarified. In one study showing a negative association between duration of obesity and fasting and 2-hour insulin concentrations, the authors suggested that a long duration of obesity might be associated with a low insulin response rather than with insulin resistance (4). The study was based on subjects with normal glucose tolerance, and the extent to which these results can be extrapolated to persons with impaired glucose tolerance or type 2 diabetes is uncertain. In another study (3), one in which no distinctions were made between normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes, no association was found between past obesity (10 years earlier) and mean insulin responses (summed at both 1 hour and 2 hours following oral glucose tolerance testing). This result might be obtained if past obesity is associated with both insulin resistance and insulin deficiency. Since one factor increases insulin responses and the other factor decreases them, the effects may cancel each other out. One advantage of this particular study is that we assessed the separate associations between obesity and indicators of insulin resistance and of decreased insulin secretion.

We found that not only did the odds ratio for insulin resistance increase with the magnitude of present obesity (17), as has been shown in previous studies (18, 19), but a dose-response relationship was seen between insulin resistance and duration of obesity. The association between obesity and insulin secretion was somewhat different. With present body mass index, the association followed a pattern similar to that found with insulin resistance—i.e., the odds ratio decreased with the magnitude of obesity. However, there was no clear association between low insulin secretion and a short duration of obesity, whereas a very marked association was seen with obesity of long duration. These results were similar independently of whether HOMA or fasting and 2-hour insulin response was used to define insulin resistance and secretion. Altogether, these findings suggest that obesity primarily affects insulin resistance, with no latency period or a relatively short latency period; when obesity is prolonged, there is also an effect on insulin secretion.

It should be recognized that our results are based on crude indicators of insulin resistance and secretion. However, the HOMA method and high fasting insulin concentrations as measures of insulin resistance correlate well with more sophisticated methods such as the euglycemic hyperinsulinemic clamp technique (7, 17, 20). In addition, use of the HOMA method for defining β-cell function has been evaluated against the hyperglycemic clamp method, with fairly good agreement being found (7). Using 2-hour insulin response can be controversial, since, in subjects with normal glucose tolerance, low insulin levels might indicate that subjects have returned to fasting levels rather than reveal a low insulin response. However, in subjects with impaired glucose tolerance, a low 2-hour insulin response has been shown to be an indicator of later development of type 2 diabetes (21-24). Accordingly, we restricted the analyses of insulin secretion to subjects with impaired glucose tolerance. With regard to the insulin resistance analyses, there was only one case in the categories with body mass index below 25.0, making the odds ratios imprecise. Strikingly, moving the cutpoint, thereby classifying the highest half of the subjects instead of the highest tertile as insulin-resistant, gave us no additional unexposed cases in the fasting insulin analyses and only two in the HOMA(resistance) analyses.

In conclusion, these results indicate that a history of overweight decreases glucose tolerance. Furthermore, our results indicate that obesity decreases glucose tolerance not only by way of insulin resistance but also, after prolonged obesity, by impairing insulin secretion. This is consistent with the hypothesis that obesity, through insulin resistance, increases the demand for insulin resistance.
insulin and that the increased demand might eventually result in decreased insulin secretion due to β-cell exhaustion (25).

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