Body Weight Patterns From 20 to 49 Years of Age and Subsequent Risk for Diabetes Mellitus

The Johns Hopkins Precursors Study

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Background: Obesity in middle age is a well-known risk factor for the development of type 2 diabetes mellitus. However, the importance of weight and weight gain at younger ages is less certain.

Objective: To determine the relationship of body weight patterns from 20 to 49 years of age with the subsequent risk for type 2 diabetes mellitus.

Setting: An ongoing longitudinal study of former medical students.

Participants: Nine hundred sixteen white men without diabetes at 50 years of age.

Measurements: Weight and height measured in medical school, then assessed by mailed questionnaire to 49 years of age.

Main Outcome: Incident type 2 diabetes mellitus based on physician self-report.

Results: During 14,255 person-years of follow-up, there were 35 incident cases of type 2 diabetes mellitus (2.5 per 1000 person-years). After simultaneous adjustment for age, physical activity, lifetime maternal history of diabetes, and smoking, body mass indexes (BMIs; calculated as weight in kilograms divided by the square of height in meters) at 25, 35, and 45 years of age were all strongly associated with diabetes risk (relative risks for overweight [BMI ≥ 25.0] vs not overweight, >3.0; all P < .05), as were maximum and average BMI to 49 years of age. The relationship of BMI at 25 years of age to diabetes risk was substantially attenuated by adjustment for BMI at 45 years of age and average BMI, but was independent of weight change, weight variability, or maximum BMI.

Conclusion: In men, overweight at 25 years of age strongly predicts diabetes risk in middle age, largely through its association with overweight at 45 years of age and high average BMI to 49 years of age.

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United States heightens the need for such information. With this in mind, we conducted a prospective cohort study with the following 2 aims: to determine the relationship between weight patterns from 20 to 49 years of age and the subsequent risk for type 2 diabetes mellitus and to compare the predictive value of these patterns.

Table 1 summarizes characteristics of the 916 men. The sample was predominantly white; the mean age at enrollment was about 23 years; by 50 years of age, fewer than 1 in 5 were current smokers; and about 25% reported diabetes in a parent during the full follow-up. By present standards, the men were lean, with a mean BMI of 23.2 at 25, 23.9 at 35, and 24.1 at 45 years of age. On average, the men gained 1 U BMI from 25 through 45 years of age. For a man of 1.8 m height (5 ft 11 in), this corresponds to a weight gain of 3.2 kg (7.1 lb). From 20 through 49 years of age, mean maximum BMI was 25.9, mean BMI variability was 2.3, and mean average BMI was 23.8.

As expected, BMIs at 25, 35, and 45 years of age were strongly associated with each other, as well as with maximum and average BMI (all rs > 0.50; all \( P < .001 \) [Table 2]). In contrast, BMI at 25 years of age was inversely associated with BMI change from 25 through 45 years of age (\( r = -0.38 \)). Variability of BMI was not strongly associated with most other features of weight history (\( -0.20 < r < 0.20 \)), except for maximum BMI (\( r = 0.47 \)).

During an average of 15.6 years (range,1-30 years) of follow-up, after 50 years of age, there were 35 incident cases of type 2 diabetes mellitus, corresponding to an incidence rate of 2.5 per 1000 person-years. Figure 1 displays a Kaplan-Meier plot of incident diabetes after 50 years of age by BMI at 25 years of age. By 65 years of age,
defined as the sum of the squared distances between the reported BMI and the BMI predicted from the random-effects model at the same age, divided by the number of reported BMI values. Finally, to reflect duration and degree of obesity, we calculated average BMI, ie, the sum of BMI values for the 30 years from 20 to 49 years of age, divided by 30. For this calculation, changes in weight between reported values separated by more than 1 year were assumed to have occurred in a single step at the midpoint between values.

**DEFINITION OF INCIDENT TYPE 2 DIABETES MELLITUS AFTER 50 YEARS OF AGE**

Incident type 2 diabetes mellitus was defined by the occurrence of any of the following conditions after 50 years of age: (1) report of pharmacologically treated diabetes on an annual mailed questionnaire; (2) report of nonpharmacologically treated diabetes on 2 or more annual mailed questionnaires; (3) physician diagnosis of diabetes in office or hospital records; (4) report of a fasting plasma glucose level of at least 7.8 mmol/L (≥140 mg/dL) or a nonfasting plasma glucose level of at least 11.1 mmol/L (≥200 mg/dL); and (5) diagnosis of diabetes as an underlying or other condition on a death certificate. (Individuals who met any of these conditions before 50 years of age were excluded from the present analysis.) Of the 35 incident cases that are the subject of this analysis, 8 (23%) were confirmed by medical records or death certificates and 25 (71%) by the completion of a supplemental diabetes questionnaire that confirmed symptoms at presentation, elevated fasting glucose or glycohemoglobin levels, and/or antidiabetic medication use and that ruled out a history of ketosis, immediate need for insulin therapy at diagnosis, or other features suggestive of type 1 diabetes mellitus. The earliest record of diabetes was taken as the event date.

**DEFINITION OF COVARIATES**

Physical activity at enrollment was classified by response to the following question: How much regular exercise have you had during the past month? (1) none, (2) little, (3) moderate, (4) much.

Cigarette smoking was defined by a time-dependent dichotomous smoking variable that reflected changes in smoking behavior during the entire follow-up. Parental history of diabetes mellitus was defined by the presence of participant report of diabetes in a parent on enrollment or at any point during follow-up or diagnosis of diabetes as an underlying or other condition of the death certificate of a participant’s parent.

**STATISTICAL ANALYSIS**

At 50 years of age, men were characterized by various patterns of body weight during the preceding 30 years. To assess the interrelatedness of these continuous variables, we constructed a matrix of Pearson correlation coefficients. Next, we investigated their relationship with the risk for incident diabetes after 50 years of age using Kaplan-Meier analyses. In these analyses, BMI change, maximum BMI, BMI variability, and average BMI were categorized into quartiles. However, to facilitate comparisons and interpretability, absolute BMIs at 25, 35, and 45 years of age were handled differently. These variables were categorized into 4 groups based on set cut points derived from the distribution of BMI at 35 years of age, then rounded to the nearest whole BMI unit (<22.0, 22.0-23.9, 24.0-24.9, and ≥25.0). The cut point at 25.0 corresponds to the present National Institutes of Health definition of overweight. The log-rank test was used to determine the statistical significance of risk differences between quartiles. We used proportional hazards regression to estimate the relationship of individual weight history features with diabetes risk independent of baseline physical activity, time-dependent smoking, and cumulative maternal history of diabetes. In this cohort, cumulative paternal diabetes from enrollment through follow-up was not associated with incident diabetes risk (data not shown). The assumption of proportionality underlying these regression models was confirmed by examining log-log plots. Finally, we assessed the independent predictive value of BMI at 25 years of age relative to other body weight measures by constructing a series of proportional hazards regression models that included selected body weight measures in addition to aforementioned covariates. All tests of significance were 2-tailed.
counterparts, diabetes was almost 1.5 times more likely to develop after 50 years of age in men with BMI of 25.0 or greater at 25 years of age. Body mass index at 35 and 45 years of age, maximum BMI, and average BMI also displayed strong predictive value (all relative risks, >3.0).

Finally, to determine the predictive value of BMI at 25 years of age independent of other BMI patterns before 50 years of age, we constructed 5 additional proportional hazards models (Table 4). In addition to age and physical activity at enrollment, maternal history of diabetes, and time-dependent cigarette smoking, each model included BMI at 25 years of age along with 1 or 2 other body weight measures. As before, relative risks for BMI at 25 years of age independent of other BMI patterns before 50 years of age, we constructed 5 additional proportional hazards models (Table 4). In addition to age and physical activity at enrollment, maternal history of diabetes, and time-dependent cigarette smoking, each model included BMI at 25 years of age along with 1 or 2 other body weight measures. As before, relative risks for BMI at 25 years of age were significantly attenuated by BMI at 35 and 45 years of age.

Table 1. Selected Characteristics of 916 Men Without Diabetes by 50 Years of Age*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>898 (98.0)</td>
</tr>
<tr>
<td>Mean ± SD, age at enrollment, y</td>
<td>22.7 ± 1.8</td>
</tr>
<tr>
<td>Physical activity at baseline†</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>383 (48.0)</td>
</tr>
<tr>
<td></td>
<td>Little</td>
</tr>
<tr>
<td></td>
<td>263 (33.0)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>127 (15.9)</td>
</tr>
<tr>
<td></td>
<td>Much</td>
</tr>
<tr>
<td></td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>Smoking status at 50 years of age‡</td>
<td>Current</td>
</tr>
<tr>
<td></td>
<td>166 (18.1)</td>
</tr>
<tr>
<td></td>
<td>Former</td>
</tr>
<tr>
<td></td>
<td>328 (35.6)</td>
</tr>
<tr>
<td></td>
<td>Never</td>
</tr>
<tr>
<td></td>
<td>421 (46.0)</td>
</tr>
<tr>
<td>Parental history of type 2 diabetes mellitus§</td>
<td>Mother</td>
</tr>
<tr>
<td></td>
<td>108 (11.8)</td>
</tr>
<tr>
<td></td>
<td>Father</td>
</tr>
<tr>
<td></td>
<td>139 (15.2)</td>
</tr>
<tr>
<td></td>
<td>Either</td>
</tr>
<tr>
<td></td>
<td>224 (24.4)</td>
</tr>
<tr>
<td>Body weight patterns before 50 years of age, mean ± SD, kg/m²</td>
<td>BMI at 25 years of age 23.2 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>BMI at 35 years of age 23.9 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>BMI at 45 years of age 24.1 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>BMI change, 25-45 years of age 1.0 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>Maximum BMI, 20-49 years of age 25.9 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>BMI variability, 20-49 years of age 2.3 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>Average BMI, 20-49 years of age 23.8 ± 2.4</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as number (percentage) of subjects. BMI indicates body mass index.
†Data available on 798 men.
‡Data available on 915 men.
§Assessed through 1995 or until death.

Table 2. Correlations Among Selected Body Weight Patterns in 916 Men Without Diabetes by 50 Years of Age*

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.63†</td>
<td>0.58†</td>
<td>0.38†</td>
<td>0.67†</td>
<td>0.14†</td>
</tr>
<tr>
<td>35 years of age</td>
<td>-</td>
<td>0.70†</td>
<td>0.14†</td>
<td>0.71†</td>
<td>0.07†</td>
</tr>
<tr>
<td>45 years of age</td>
<td>-</td>
<td>-</td>
<td>0.54†</td>
<td>0.83†</td>
<td>0.15†</td>
</tr>
<tr>
<td>Maximum BMI, 20-49 years of age</td>
<td>-</td>
<td>-</td>
<td>0.25†</td>
<td>0.02</td>
<td>0.14†</td>
</tr>
<tr>
<td>BMI variability, 20-49 years of age</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.47†</td>
<td>0.90†</td>
</tr>
</tbody>
</table>

*All results are shown as Pearson correlation coefficients. BMI indicates body mass index.
†P < .001.
‡P < .05.

These data suggest that, among white men, overweight at 25 years of age is a strong predictor of incident type 2 diabetes mellitus in middle age. This association appears to be explained largely by subsequent tracking of BMI to 49 years of age. Differences in BMI below 25.0 at 25 years of age did not appear to predict incident diabetes. These data also suggest that overweight at 45 years of age and average BMI before 50 years of age are the weight patterns most strongly associated with diabetes risk in middle age, followed by BMI at 25 years of age. A unique strength of our study was its use of 3 decades of prospectively collected data on body weight to characterize body weight patterns in early adulthood up to 50 years of age.

Several limitations of our study also deserve comment. First, by design the sample is limited to physicians who, for historical reasons, were almost entirely white men. This group is at relatively low risk for obesity and type 2 diabetes mellitus. Our results are therefore not directly generalizable to women, to individuals of lower socioeconomic status, or to members of ethnic minority groups, especially with regard to absolute levels of risk. Second, with the exception of the baseline measurement, we relied on self-report to characterize body weight. In this cohort of former medical students, self-report was quite accurate. However, to the extent that...
there was random misclassification, or a bias toward underreporting at higher levels of weight, we may have underestimated the true association between higher body weight and diabetes risk in our cohort. Third, ascertainment of incident diabetes was based only on self-report of physician diagnosis; the wide national dispersion of the cohort precluded the collection of blood specimens that would have greatly enhanced the sensitivity of ascertainment. No doubt, suboptimal sensitivity reduced the precision of our results. More important is the theoretical concern that suboptimal sensitivity may have led to ascertainment bias insofar as overweight men were more likely to be screened for diabetes than their leaner counterparts. In fact, it seems unlikely that body weight patterns before 50 years of age might influence screening practice years or even decades later. Finally, the relatively small number of incident diabetes cases (n = 35) limited the study's statistical power and, therefore, the precision of its risk estimates.

Since 1970, at least 28 studies have confirmed a strong relationship between body weight and the risk for type 2 diabetes mellitus.13,25-30 In most of these studies, body weight was first assessed at 40 years of age and older; only 6 assessed body weight at younger ages.13,17,25,28-30 Two studies based on the Pima Indians25,29 used prospectively collected biennial data on weight from as early as 15 years of age to examine the following 3 aspects of weight history: duration of obesity,25 weight gain,29 and weight fluctuation.20 In this population at unusually high risk for obesity and type 2 diabetes mellitus, duration of obesity was a strong predictor of type 2 diabetes mellitus in men and women,25 as was weight gain in nonoverweight individuals.20 In overweight Pima Indians, weight gain predicted diabetes in men, but not women.20 However, baseline overweight status was a strong predictor of diabetes risk independent of weight gain. In contrast, weight fluctuation was not associated with diabetes risk in either sex.20 Although these analyses did not explicitly address the relative predictive value of body weight in young adulthood vs middle age, they appear to be generally consistent with our results.

Unlike the studies of the Pima Indians, 2 studies of predominantly white populations relied largely17,26 or exclusively15 on retrospective weight data before 40 years of age, asking participants in the fifth, sixth, and seventh decades to recall weight at 18 years of age. In 1989, Holbrook et al15 described 886 men and 1114 women aged 50 years and older in Rancho Bernardo, Calif. Neither self-perceived overweight nor recalled body weight at 18 years of age was associated with diabetes. Instead, self-perceived underweight at 18, weight gain from 18 to 40, and recalled weight gain and weight fluctuation from 40 to 60 years of age and recalled maximum lifetime weight were significantly associated with diabetes. However, since diabetes may have developed and been diagnosed before exposure assessment in many participants, the possibility of recall bias or reverse causality cannot be excluded.

Colditz and colleagues17,26 have presented 8- and 14-year follow-up results in more than 90 000 initially nondiabetic women aged 30 to 55 years in the Nurses Health Study who provided data on recalled weight at 18 years of age. In both analyses, BMI at 18 years of age was strongly
associated with the development of diabetes after enrollment, as was weight gain from 18 years of age to enrollment. However, the relationship of BMI at 18 years of age with diabetes risk was completely dependent on BMI at enrollment. These findings are similar to ours.

Finally, Ford and colleagues recently published results from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study regarding the risk for diabetes related to body weight and weight gain in a biracial cohort of men and women, 3,300 of whom were aged 18 to 39 years at baseline. In this national sample, BMI at baseline and weight gain during the first 10 years of follow-up were strong predictors of incident diabetes during the second 10 years of follow-up. Although the authors reported no interaction between age and weight or weight gain, the study lacked longitudinal data required to compare the predictive strength of body weight in young adulthood directly vs middle age within individuals.

Of the numerous studies of overweight and obesity in childhood, 2 have addressed diabetes in middle age directly vs middle age within individuals. However, the relationship of BMI at 18 years of age with diabetes risk was completely dependent on BMI at enrollment. These findings are similar to ours.

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Of the numerous studies of overweight and obesity in childhood, 2 have addressed diabetes in middle age as an outcome. In a sample of 716 residents of Hagerstown, Md, Abraham and colleagues found weak relationships of overweight at 9 to 13 years of age with fasting glucose levels and prevalent diabetes 30 to 40 years later, but these relationships were not statistically significant. Likewise, Mossberg observed a higher incidence of diabetes in 504 Swedes who had been hospitalized for obesity during childhood (7.4%), compared with a population-based reference group (2.3%), although the difference was not statistically significant. Both studies were limited by small numbers and relatively high numbers of patients unavailable for follow-up. Neither assessed the predictive value of childhood overweight independent of overweight in adulthood.

The possibility of some residual association of BMI at 25 years of age with diabetes risk after adjustment for BMI at 45 years of age and average BMI raises a question about biological mechanism. One possible explanation is that early adulthood marks the end of a critical period for the development of metabolism. For example, androgen-induced intra-abdominal fat deposition during adolescence may contribute to subsequent hepatic insulin resistance that, in turn, leads to glucose intolerance. Another possibility is that differences in body weight in early adulthood reflect genetic predisposition to a greater extent than differences in middle age. To the extent that diabetes and overweight share common genetic risk factors, overweight in young adulthood would appear to itself confer risk, while in fact merely serving as a phenotypic marker. However, were this hypothesis true, one might have predicted that adjustment for parental history of diabetes would have attenuated the as-
In our study, this association appeared to be independent of parental diabetes history.

Finally, overweight in young adulthood may confer diabetes risk by adding to cumulative exposure. In most epidemiological studies of adults, body weight has been analyzed independent of time. The only study that specifically investigated duration of obesity found it to be a strong risk factor for type 2 diabetes mellitus. In our study, much of the predictive value of BMI at 25 years of age was mediated by its association with a time-weighted average of body mass, a characterization of exposure that combines duration and degree. It may be that measurements of BMI confined to early middle age simply miss an important early contribution to cumulative exposure, like beginning assessment for pack-years of cigarette smoking at 40 rather than at 20 years of age. If sustained for decades, the insulin resistance associated with high body weight could contribute to the exhaustion of the ability of islet cells to maintain compensatory hyperinsulinemia, and thereby hasten the onset of diabetes.

Our study has 3 main implications. First, it suggests that future research on the relationship between body weight and diabetes risk should consider body weight in young adulthood and its relationship to average body weight through early middle age. Second, it implies that interventions aimed at the primary prevention of type 2 diabetes mellitus via weight control and weight reduction might be targeted at overweight young adults as well as overweight middle-aged individuals. Finally, it suggests that, in the absence of effective prevention strategies, the rising prevalence of overweight in young adults today may accelerate the incidence of diabetes well into the next century.

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REFERENCES