# Obesity, Fat Distribution, and Weight Gain as Risk Factors for Clinical Diabetes in Men

JUNE M. CHAN
ERIC B. RIMM, SCD
GRAHAM A. COLDITZ, MD
MEIR J. STAMPFER, MD
WALTER C. WILLETT, MD

**OBJECTIVE** — To investigate the relation between obesity, fat distribution, and weight gain through adulthood and the risk of non-insulin-dependent diabetes mellitus (NIDDM).

**RESEARCH DESIGN AND METHODS** — We analyzed data from a cohort of 51,529 U.S. male health professionals, 40–75 years of age in 1986, who completed biennial questionnaires sent out in 1986, 1988, 1990, and 1992. During 5 years of follow-up (1987–1992), 272 cases of NIDDM were diagnosed among men without a history of diabetes, heart disease, and cancer in 1986 and who provided complete health information. Relative risks (RRs) associated with different anthropometric measures were calculated controlling for age, and multivariate RRs were calculated controlling for smoking, family history of diabetes, and age.

**RESULTS** — We found a strong positive association between overall obesity as measured by body mass index (BMI) and risk of diabetes. Men with a BMI of ≥35 kg/m$^2$ had a multivariate RR of 42.1 (95% confidence interval [CI] 22.0–80.6) compared with men with a BMI <23.0 kg/m$^2$. BMI at age 21 and absolute weight gain throughout adulthood were also significant independent risk factors for diabetes. Fat distribution, measured by waist-to-hip ratio (WHR), was a good predictor of diabetes only among the top 5%, while waist circumference was positively associated with the risk of diabetes among the top 20% of the cohort.

**CONCLUSIONS** — These data suggest that waist circumference may be a better indicator than WHR of the relationship between abdominal adiposity and risk of diabetes. Although early obesity, absolute weight gain throughout adulthood, and waist circumference were good predictors of diabetes, attained BMI was the dominant risk factor for NIDDM; even men of average relative weight had significantly elevated RRs.

From the Department of Epidemiology (E.B.R., M.J.S., W.C.W.) and the Department of Nutrition (J.M.C., E.B.R., M.J.S., W.C.W.), Harvard School of Public Health; and the Channing Laboratory (G.A.C., M.J.S., W.C.W.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Eric B. Rimm, ScD, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115.

Received for publication 6 December 1993 and accepted in revised form 7 April 1994.

NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; WHR, waist-to-hip ratio; RR, relative risk; CI, confidence interval.

Risk of non-insulin-dependent diabetes mellitus (NIDDM) has been strongly associated with obesity (1–18). Metabolic studies suggest that obesity is accompanied by a reduced number of insulin receptors as well as insulin resistance (19–22). This alteration in glucose metabolism is, however, reversible with weight loss (23–24). Thus, it is widely accepted that obesity is causally related to NIDDM (6). Other studies also suggest that abdominal obesity specifically increases the risk of diabetes (19,21,25–27).

In the Nurses' Health Study, a strong quantitative relationship was observed between body mass index (BMI) (a measure of obesity) and the risk of diabetes among women (1). Even women with a BMI between 23 and 24 kg/m$^2$, which is less than the population average, had a risk of diabetes 3.6 times that of women with BMIs <22 kg/m$^2$. It was also suggested that the amount of weight gained since early adulthood significantly contributed to the risk of acquiring diabetes in later life.

Previous studies have found BMI and fat distribution to be independent risk factors for diabetes in men. However, the emphasis put on weight distribution as a strong predictor for diabetes, independent of BMI, may be misplaced because the statistical control for BMI has been incomplete in many studies. The present investigation prospectively examined finely divided strata of BMI and waist-to-hip ratio (WHR) (a measure of fat distribution) to determine more precisely at what levels the risk of diabetes is increased in a large cohort of U.S. men. Absolute weight gain since early adulthood was also examined as a potential risk factor for diabetes.

## RESEARCH DESIGN AND METHODS

— The Health Professionals' Follow-up Study began in 1986 as a prospective study, primarily investigating the risk factors for cardiovascular disease and cancer. The cohort was comprised of

51,529 males, 40–75 years of age, who completed a six-page baseline questionnaire in 1986. The cohort includes men from six different health occupations: dentists, veterinarians, osteopaths, podiatrists, optometrists, and pharmacists. Further details of the cohort and follow-up techniques can be found elsewhere (28).

We obtained information from the 1986 baseline questionnaire on current height and weight, medical history, past and present smoking habits, family history of various diseases, heart disease risk factors, weight at age 21, and weight change in the past 5 years. Biennial questionnaires sent out in 1988, 1990, and 1992 were used to update exposure information and to ascertain newly diagnosed cases of diabetes.

Family history of diabetes was obtained by a brief follow-up questionnaire sent out in 1987. In addition, we included paper tape measures to assist the men in self-reporting their waist and hip circumferences. Men were asked to take measurements while standing and to avoid measuring over bulky clothing. They were instructed to measure their waists at the umbilicus and to take their hip measurement as the largest circumference between the waist and thighs; illustrations were included with the directions. Because the 1987 questionnaire was not part of the usual biennial mailings, we did not use extensive follow-up procedures (29) to increase our follow-up rate to >65%. In 1990, Rimm et al. (30) found self-measured waist, hip, and weight measurements to be reasonably valid when compared with standardized measurements by a technician in a subset of this cohort. The crude Pearson correlation between self-reported waist circumferences and the average of two technician-measured waist circumferences was 0.95 for men; the analogous correlation for hip circumference was 0.88. The differences in mean circumference (technician measured minus self-measured) were 0.36 inches for waist and −0.78 inches for hips. Self-reported and measured weights were strongly correlated ($r$ = 0.97, mean difference −2.34 lbs). The correlation between self- and technician-measured WHRs was 0.69 with a mean difference of 0.027. After adjusting for age and BMI and correcting for random within-person variability from daily or seasonal fluctuations, the correlation for WHR was 0.62. Although not validated in this population, self-reporting by middle-aged men of weight in early adulthood has also been shown to be moderately accurate ($r$ = 0.80) (31). Weight and height were reported in pounds and inches and were converted to metric units to calculate BMI. In this cohort, waist and hip circumferences were correlated with height. Thus, to investigate the associations of these measures independent of height, we calculated height-adjusted waist and hip circumferences as the residuals using separate least-squares regression models with height as the independent variable and the circumference measure as the dependent variable. To make the residuals interpretable, we added the population mean circumference to each of the residuals. This procedure removed variation in waist or hip circumferences due to height.

### Population for analysis

Among the 51,529 men in the Health Professionals' Study, 44,018 had provided complete medical history information and were free of diabetes, coronary heart disease, and cancer in 1986. Of these, 15,496 did not provide complete waist and hip circumference measurements, and an additional 539 did not provide complete weight or height information in 1986 and were excluded from the study population. The remaining 27,983 men comprised the population for analysis.

We confirmed a diagnosis of diabetes from information collected from a supplementary questionnaire, which was sent to those participants who indicated having a new diagnosis of diabetes on the 1988, 1990, or 1992 questionnaire. We classified a person as having incident NIDDM if he met one of the following criteria: *1*) he reported one or more classic symptoms (thirst, polyuria, weight loss, hunger, or pruritus), plus fasting plasma glucose at least 140 mg/dl or random plasma glucose at least 200 mg/dl; or 2) at least two elevated plasma glucose concentrations on different occasions (fasting at least 140 mg/dl and/or random at least 200 mg/dl and/or concentration at least 200 mg/dl after ≥2 hours on oral glucose tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). These criteria were in accordance with those of the National Diabetes Data Group (32). After exclusions, we confirmed 272 new cases of NIDDM from the 290 subjects who reported diabetes and returned a supplementary questionnaire.

The validity of self-reported diabetes using the same supplementary questionnaire has been studied in the Nurses' Health Study. Medical records were obtained from 62 women, who were selected at random, reporting diabetes and classified as definite NIDDM by a supplementary questionnaire. Sixty-one of the 62 women classified as having NIDDM by questionnaire response were confirmed by medical record review (1).

### Data analysis

We used BMI (kg/m$^2$) as a measure of relative weight. The range of BMI was divided into nine categories with whole number cutoff points. Participants contributed person-months of follow-up time starting from the return of the 1987 questionnaire until the date of diabetes diagnosis, date of death, or until 31 January 1992.

In this study, incidence rates were calculated by dividing the number of incident cases by the number of total person-years of follow-up for each category of BMI. Relative risks (RRs) were then computed by dividing the incidence rates for a specific category by the incidence rate of the lowest category, adjusting for age in each model (33). To distinguish between the effects of early BMI and cur-

**Table 1—*BMI and risk of diabetes among a cohort of 27,983 U.S. men aged 40–75 years in 1986 followed for 5 years***

| BMI categories | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Range (kg/m$^2$) | <23 | 23.0–23.9 | 24.0–24.9 | 25.0–26.9 | 27.0–28.9 | 29.0–30.9 | 31.0–32.9 | 33.0–34.9 | ≥35 |
| Person-years | 25,488 | 20,190 | 18,384 | 34,230 | 17,402 | 7,427 | 3,140 | 1,351 | 870 |
| Cases | 17 | 13 | 20 | 55 | 57 | 38 | 27 | 21 | 24 |
| Age-adjusted RR | 1.0 | 1.0 (0.5–2.0) | 1.6 (0.8–3.1) | 2.3 (1.4–4.0) | 4.8 (2.9–8.0) | 8.1 (4.9–13.5) | 13.8 (8.5–22.3) | 26.9 (17.1–42.5) | 50.7 (34.6–74.4) |
| Multivariate RR | 1.0 | 1.0 (0.5–2.0) | 1.5 (0.8–2.9) | 2.2 (1.3–3.8) | 4.4 (2.6–7.7) | 6.7 (3.8–12.0) | 11.6 (6.3–21.5) | 21.3 (11.4–41.2) | 42.1 (22.0–80.6) |
| Multivariate RR with WHR | 1.0 | 0.9 (0.4–1.8) | 1.4 (0.7–2.7) | 1.9 (1.1–3.3) | 3.6 (2.1–6.3) | 5.2 (2.9–9.5) | 8.8 (4.7–16.7) | 15.5 (7.8–30.7) | 31.7 (16.2–62.0) |

Data are RR (95% CI). Multivariate RR model controls for age in 5-year intervals, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, ≥25 cigarettes/day), and family history. Multivariate RR with WHR model controls for age in 5-year intervals, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), family history, and quintiles of WHR.

rent BMI, we classified men jointly by relative weight at age 21 and categories of weight gain since age 21. To adjust for other risk factors, we used multiple logistic regression to generate odds ratios as an estimate of RR. Multivariate logistic regression models were used to examine BMI and other anthropometric measures in relation to risk of diabetes after controlling for age, smoking, and family history of diabetes.

**RESULTS** — Risk of diabetes increased continuously with increasing levels of BMI. Men with a BMI of 25.0–26.9 kg/m$^2$ had a risk 2.2 times (95% confidence interval (CI) 1.3–3.8) greater than men with a BMI <23.0 kg/m$^2$ after adjusting for age, family history, and smoking habits. Risk rose markedly for men with a BMI ≥29 kg/m$^2$. As expected, the men in the highest category, BMI ≥35.0 kg/m$^2$, had the highest RR (multivariate RR = 42.1, 95% CI 22.0–80.6) (Table 1).

When WHR was added to the standard model (controlling for family history, age, and smoking), the RRs associated with nine categories of BMI were only modestly attenuated. For example, men in the highest category of BMI had a multivariate RR of 42.1 (95% CI 22.0–80.6) before and 31.7 (95% CI 16.2–62.0) after controlling for WHR (Table 1).

To examine the relation between early adult obesity and diabetes risk, BMI at age 21 was calculated. The age-adjusted RR for men with a BMI ≥27.0 kg/m$^2$ at age 21 was 2.9 (95% CI 2.0–4.2). BMI at age 21 was moderately correlated with current BMI ($r$ = 0.61). When the model was modified to control for weight gain since age 21, age, family history, and smoking habits, the risk associated with BMI at age 21 increased. Compared with men in the lowest quintile, men with a BMI between 23.0 and 24.9 kg/m$^2$ at age 21 had an increased risk of 1.5 (95% CI 1.1–2.2), and men with a BMI ≥27.0 kg/m$^2$ at age 21 had an RR of 6.4 (95% CI 4.3–9.5) (Table 2).

Absolute weight gain throughout adulthood was also examined. Men who

**Table 2—*BMI at age 21 and risk of diabetes among a cohort of 27,338 U.S. men age 40–75 years in 1986 and followed for 5 years***

| Range (kg/m$^2$) | Person-years | Cases | Age-adjusted RR (95% CI) | Multivariate RR (95% CI) |
|---|---|---|---|---|
| BMI at age 21 | | | | |
| <21.0 | 29,085 | 69 | 1.0 | 1.0 |
| 21.0–22.9 | 36,891 | 50 | 0.6 (0.4–0.9) | 1.0 (0.7–1.4) |
| 23.0–24.9 | 33,649 | 55 | 0.8 (0.6–1.2) | 1.5 (1.1–2.2) |
| 25.0–26.9 | 17,775 | 44 | 1.2 (0.8–1.8) | 2.5 (1.7–3.8) |
| 27.0+ | 8,357 | 48 | 2.9 (2.0–4.2) | 6.4 (4.3–9.5) |
| Weight gain since age 21 | | | | |
| Loss 3+ | 9,885 | 4 | 0.5 (0.2–1.5) | 0.3 (0.1–0.8) |
| Loss 2–gain 2 | 26,261 | 19 | 1.0 | 1.0 |
| Gain 3–5 | 22,787 | 14 | 0.8 (0.4–1.6) | 0.9 (0.5–1.8) |
| Gain 6–7 | 12,987 | 17 | 1.7 (0.9–3.1) | 1.9 (1.0–3.7) |
| Gain 8–9 | 11,621 | 29 | 3.0 (1.8–5.2) | 3.5 (2.0–6.3) |
| Gain 10–14 | 20,964 | 48 | 2.6 (1.5–4.3) | 3.4 (2.0–5.8) |
| Gain 15+ | 24,019 | 141 | 6.5 (4.4–9.6) | 8.9 (5.5–14.7) |

Analysis includes 27,338 participants (266 cases) with complete information on BMI at age 21. Multivariate RR model for BMI at age 21 controls for age in 5-year intervals, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and seven categories of weight change since age 21. Multivariate RR model for weight gain since age 21 controls for age, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and quintiles of BMI at age 21.

had gained 6–7 kg since age 21 had an increased multivariate RR of diabetes (RR = 1.9, 95% CI 1.0–3.7) compared with men with an absolute weight change <2 kg after controlling for age, smoking, family history, and BMI at age 21. A model was also constructed including tertiles of BMI at age 21 and weight gain since age 21, controlling for age, family history, and smoking. Across the range of BMI, absolute weight gain was positively associated with the risk of diabetes. Risk increased within each tertile of weight gain as well as within each category of BMI at age 21 (Fig. 1; Table 2).

Recent weight gain was strongly associated with the risk of diabetes. Information was available on weight gained in the 5 years before 1986 for 259 of the 272 NIDDM cases. After controlling for BMI in 1981, family history, age, and smoking habits, men who had gained ≥13.6 kg (the equivalent of ≥30 lbs) had a risk 4.5 times that of men who were within 4.5 kg of their 1981 weight (95% CI 2.4–8.2) (Table 3). The positive association between weight gain in the last 5 years and risk of diabetes was not appreciably modified by BMI in 1981.

We examined the waist-to-hip circumference ratio and the independent association of waist and hip circumferences and height with the risk of diabetes using three different models: controlling for age only; controlling for age, smoking, and family history of diabetes; and controlling for age, smoking, family history of diabetes, and BMI in 1986 (Table 4). We examined the RRs associated with height-adjusted hip circumference and both crude and height-adjusted waist circumference. Compared with men with a WHR <0.90, men with a WHR >0.99 (top 20%) had a multivariate RR of 4.0 (95% CI 2.5–6.2). However, after further controlling for current BMI, the multivariate RR was markedly attenuated, RR = 1.7 (95% CI 1.1–2.7).

To investigate further the effect of fat distribution on men in the highest quintile of WHR, the group was subdivided into the top 10–20%, top 5–10%, and top 5%. Compared with men in the lowest quintile of WHR, men in the top 5% of WHR had a multivariate RR of 5.2 (95% CI 3.1–8.6) and a RR of 2.0 (95% CI 1.2–3.5) after further control for BMI. WHR, independent of BMI, maintained a significant positive association to the risk of diabetes only among the top 5%. Thus, the RR of diabetes among men in the top quintile (top 20%) of WHR, observed originally in Table 4, is primarily attributable to the top quarter of that group (the top 5% of the cohort).

Men with a crude waist circumference >40.0 inches (top 20%) had a multivariate RR of 10.8 (95% CI 6.2–18.7), but this was reduced to 3.5 (95% CI 1.7–7.0) after control for BMI. Men in the highest quintile of height-adjusted waist circumference had a multivariate RR of 9.8 (95% CI 5.6–17.0) and 3.1 (95% CI 1.4–6.6) after adding BMI to the model. Hip circumference was positively associated with risk of diabetes in the multivariate model (RR = 7.3, 95% CI 4.4–12.0); however, after control for BMI in 1986, hip circumference was not a significant risk factor. No association between height and risk of diabetes was observed. However, absolute weight was found to be independently correlated to risk of diabetes for the highest quintile group, even after controlling for current relative weight, age, smoking, and family history (RR = 2.1, 95% CI 1.0–4.4 for men weighing 198–307 lbs). Overall, current BMI prevailed as the strongest predictor of diabetes when included together in a model with hip circumference, height measurements, or WHR.

The WHR, which is associated with diabetes, is commonly used as an indicator of abdominal fat. Waist circumference, because it is a single measurement, contributes less error than WHR, and, particularly when adjusted for height, may be a more direct measure of abdominal fat. The RRs associated with abdominal adiposity were examined more closely by subdividing the top 20% of waist measurement into quartiles. The incidence rate associated with each quar-

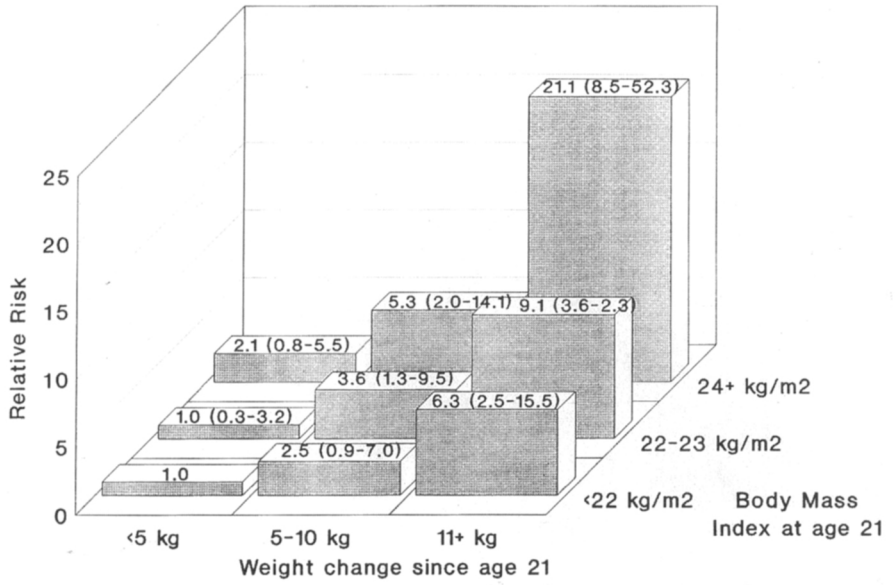


**Figure 1**—*The RR increases shown within each tertile of weight gain and within each category of BMI at age 21.*

tile of the top 20% was compared with that of men in the lowest quintile of the whole cohort. There was no substantial difference between the risk of diabetes associated with crude waist measurements and that associated with height-adjusted waist measurements. Increased RRs were seen for each quartile group within the top 20% even in multivariate models adjusted for BMI. Men with a height-adjusted waist measurement >43.8 inches (top 5%) had a multivariate RR of 18.6 (95% CI 10.4–33.3) compared with men with a waist measurement <34.75 inches; risk was attenuated after further controlling for BMI (RR = 4.3, 95% CI 1.9–10.1).

We calculated RRs of diabetes for BMI and WHR within strata of age (Table 5). After controlling for WHR and other confounders, we found that men age 40–49 with a BMI ≥35 kg/m$^2$ had a RR of diabetes of 77.4 (95% CI 25.2–247.0); men aged ≥60 in the same category of BMI had a much lower RR (RR = 14.9, 95% CI 4.3–52.1). Conversely, older men in the top quintile of WHR had a much higher RR than younger men.

The association of family history with diabetes incidence was examined prospectively. Men who had fathers, mothers, or a sibling with a history of diabetes were considered to have a positive family history of diabetes. Controlling for current relative weight of the participant, age, and smoking, men with a family history of diabetes had an elevated RR of 2.3 (95% CI 1.8–3.0) compared with men without a family history of diabetes.

Excluded from the population for analysis were 15,496 men who did not provide complete waist and hip circumference measurements. To explore the possibility that the remaining study population differed in their relation between BMI and risk of diabetes, we calculated the multivariate RR for BMI limited to those 15,496 men who did not report complete waist or hip circumference information. After excluding those men with heart disease or cancer in 1986, 182 cases of NIDDM occurred among this group. Among this subset, risk for diabetes associated with nine categories of BMI was very similar to those of the original population for analysis. Men with a BMI ≥35.0 kg/m$^2$ had a RR of 34.9 (95% CI 12.6–97.0).

We considered the possibility that diagnostic bias may account for the relationship observed between BMI and the risk of diabetes. It is possible that physicians, aware of the associations between obesity and diabetes, may be more likely to diagnose diabetes in assymptomatic

**Table 3**—*Weight change between 1981 and 1986 among men who self-reported anthropometric measurements*

| Weight change 1981–1986 (kg) | BMI <28 kg/m$^2$ in 1981 | | | BMI ≥28 kg/m$^2$ in 1981 | | | RR (95% CI) adjusted for BMI in 1981 |
|---|---|---|---|---|---|---|---|
| | Cases | Person-years | Age-adjusted RR (95% CI) | Cases | Person-years | Age-adjusted RR (95% CI) | |
| Lost 4.5+ | 10 | 5,772 | 1.5 (0.8–2.9) | 15 | 3,326 | 0.7 (0.4–1.2) | 0.8 (0.5–1.2) |
| Lost 4.5–gain 4.5 | 105 | 89,104 | 1.0 | 58 | 8,526 | 1.0 | 1.0 |
| Gain 4.5–13.6 | 25 | 13,947 | 1.7 (1.1–2.6) | 33 | 2,901 | 1.8 (1.2–2.8) | 1.7 (1.2–2.3) |
| Gain 13.6+ | 4 | 868 | 4.6 (1.8–11.3) | 9 | 328 | 4.8 (2.5–9.2) | 4.5 (2.4–8.2) |

Analysis includes 27,159 participants (259 cases) with complete information on BMI in 1981/weight change; uneven cutoff points caused by conversion from pounds to kilograms. RR adjusted for age in 5-year intervals, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and deciles of BMI in 1981.

Table 4—*Waist, hips, height, and WHR in 1986 as risk factors for diabetes*

| | Quintiles | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Waist (crude) | | | | | |
| Range (inches) | 29.4–34.5 | 34.6–36.0 | 36.1–38.0 | 38.1–40.0 | 40.1–69.0 |
| Cases | 14 | 26 | 38 | 39 | 155 |
| Model 1: across age | 1.0 | 2.0 (1.0–3.8) | 2.2 (1.2–4.1) | 3.3 (1.8–6.0) | 12.0 (7.8–18.4) |
| Model 2: without BMI | 1.0 | 1.9 (1.0–3.7) | 2.2 (1.2–4.1) | 3.2 (1.7–5.8) | 10.8 (6.2–18.7) |
| Model 3: with BMI | 1.0 | 1.7 (0.9–3.3) | 1.7 (0.8–3.3) | 1.9 (0.9–3.9) | 3.5 (1.7–7.0) |
| Waist (height-adjusted) | | | | | |
| Range (inches) | 26.9–34.5 | 34.6–36.2 | 36.3–37.9 | 37.9–40.1 | 40.2–68.3 |
| Cases | 14 | 21 | 32 | 47 | 158 |
| Model 1: across age | 1.0 | 1.37 (0.7–2.7) | 1.9 (1.0–3.7) | 2.9 (1.6–5.2) | 11.0 (7.1–17.0) |
| Model 2: without BMI | 1.0 | 1.3 (0.7–2.7) | 2.0 (1.0–3.7) | 2.8 (1.5–5.1) | 9.8 (5.6–17.0) |
| Model 3: with BMI | 1.0 | 1.2 (0.6–2.4) | 1.5 (0.7–3.0) | 1.7 (0.8–3.5) | 3.1 (1.4–6.6) |
| Hips (height-adjusted) | | | | | |
| Range (inches) | 28.1–37.7 | 37.7–39.0 | 39.0–40.1 | 40.1–41.7 | 41.7–64.4 |
| Cases | 17 | 26 | 39 | 55 | 135 |
| Model 1: across age | 1.0 | 1.5 (0.8–2.7) | 2.1 (1.2–3.6) | 30.0 (1.8–5.0) | 7.7 (5.1–11.8) |
| Model 2: without BMI | 1.0 | 1.5 (0.8–2.7) | 2.0 (1.1–3.6) | 2.9 (1.7–5.1) | 7.3 (4.4–12.0) |
| Model 3: with BMI | 1.0 | 1.3 (0.7–2.4) | 1.3 (0.7–2.5) | 1.4 (0.7–2.7) | 1.5 (0.7–2.9) |
| Height | | | | | |
| Range (inches) | 41–68 | 69–70 | 70–71 | 71–72 | 73–91 |
| Cases | 71 | 75 | 41 | 35 | 50 |
| Model 1: across age | 1.0 | 1.0 (0.7–1.4) | 1.1 (0.8–1.7) | 1.0 (0.7–1.6) | 1.2 (0.8–1.7) |
| Model 2: without BMI | 1.0 | 1.0 (0.7–1.4) | 1.2 (0.8–1.7) | 1.1 (0.7–1.6) | 1.2 (0.9–1.8) |
| Model 3: with BMI | 1.0 | 1.1 (0.8–1.5) | 1.3 (0.9–1.9) | 1.1 (0.7–1.6) | 1.3 (0.9–1.8) |
| WHR | | | | | |
| Range | <0.90 | 0.90–0.92 | 0.93–0.95 | 0.96–0.98 | 0.99+ |
| Cases | 24 | 24 | 46 | 68 | 110 |
| Model 1: across age | 1.0 | 0.9 (0.5–1.6) | 1.9 (1.1–3.1) | 2.5 (1.6–4.1) | 4.6 (3.0–7.0) |
| Model 2: without BMI | 1.0 | 0.9 (0.5–1.6) | 1.8 (1.1–3.0) | 2.5 (1.5–3.9) | 4.0 (2.5–6.2) |
| Model 3: with BMI | 1.0 | 0.8 (0.4–1.4) | 1.3 (0.8–2.2) | 1.4 (0.9–2.4) | 1.7 ((1.1–2.7) |

Data are RR (95% CI). Model 1, RR across age-groups; Model 2, RR controlling for age in 5-year intervals, family history, and smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day); Model 3, RR controlling for age in 5-year intervals, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and nine categories of BMI in 1986. Height-adjusted waist and hips models 2 and 3 control for height using residual analysis.

fatter men. However, when we only included the 175 cases with symptomatic diabetes, the RR associated with a BMI ≥35 kg/m$^2$ compared with a BMI <23 kg/m$^2$ (RR = 46.6, 95% CI 21.4–101.6) was actually higher than when assymptomatic cases were included.

When men who reported cancer or heart disease at baseline were added back to the population for analysis, the results were not appreciably different from those presented above.

**CONCLUSIONS** — We found an extremely strong association between BMI and risk of NIDDM. Increased risks were seen for all BMI levels ≥24.0 kg/m$^2$, well below the standard criteria for obesity. Thus, even men of average weight are substantially more likely to develop diabetes than men with a BMI <23.0 kg/m$^2$. The extremely strong RR for men with a BMI >29.0 kg/m$^2$ combined with metabolic data and the effect of weight loss on glucose tolerance warrant the conclusion that the relationship between obesity and risk of diabetes is causal (6,19–22).

The validity of BMI as a measure of body fatness or adiposity has been assessed by comparison with densitometry. Correlation coefficients with percent body fat have generally been between 0.6 and 0.8 (34). However, the correlation was >0.9 when compared with absolute fat mass adjusted for height, which appears to be a stronger predictor of glucose intolerance than percent body fat. To the

Table 5—*BMI, WHR, and risk of diabetes within age strata in 1986*

| | Multivariate RR (95% CI) | | |
|---|---|---|---|
| | Age range (years) | | |
| | 40–49 | 50–59 | 60–75 |
| *n* | 49 | 97 | 126 |
| BMI | | | |
| <23.0 | 1.0 | 1.0 | 1.0 |
| 23.0–23.9 | 0.5 (0.1–2.7) | 1.8 (0.3–10.6) | 0.9 (0.3–2.3) |
| 24.0–24.9 | 0.9 (0.2–4.0) | 2.9 (0.6–14.6) | 1.4 (0.6–3.3) |
| 25.0–26.9 | 1.2 (0.4–4.0) | 4.8 (1.1–20.5) | 1.7 (0.8–3.5) |
| 27.0–28.9 | 1.1 (0.3–4.7) | 13.3 (3.2–56.2) | 2.6 (1.2–5.6) |
| 29.0–30.9 | 4.3 (1.2–15.8) | 14.3 (3.3–63.2) | 4.2 (1.9–9.5) |
| 31.0–32.9 | 9.7 (2.5–36.7) | 23.0 (4.9–107.0) | 7.2 (3.0–17.5) |
| 33.0–34.9 | 21.2 (5.4–82.9) | 44.8 (9.5–211.7) | 8.4 (2.9–24.7) |
| ≥35.0 | 77.4 (25.2–247.0) | 42.6 (8.3–218.5) | 14.9 (4.3–52.1) |
| WHR | | | |
| <0.90 | 1.0 | 1.0 | 1.0 |
| 0.90–0.92 | 0.6 (0.2–1.6) | 1.2 (0.5–3.1) | 0.6 (0.2–1.8) |
| 0.93–0.95 | 1.0 (0.4–2.7) | 1.3 (0.5–3.3) | 1.7 (0.7–4.1) |
| 0.96–0.98 | 0.6 (0.2–1.7) | 1.2 (0.5–2.9) | 2.2 (1.0–5.1) |
| 0.99+ | 0.9 (0.4–2.2) | 2.3 (1.0–5.3) | 1.8 (0.8–4.2) |

Multivariate RR model for BMI controls for age in 5-year intervals, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and quintiles of WHR. Multivariate RR model for WHR controls for age in 5-year intervals, family history, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), and nine categories of BMI in 1986.

extent that BMI is an imperfect measurement of adiposity, the extremely strong association between BMI and risk of diabetes observed is an underestimate of this association.

As stated in METHODS, in this cohort, self-reported circumferences contain random error, especially when calculating WHR, because this ratio has reduced between-person variation and includes error from both circumference measurements. In our validation study, the correlation between the self-reported and the average of two technician-measured assessments, taken 7 months apart, was 0.62 for the WHR. A correlation of 0.62 is comparable to that found between repeat measures of blood pressure and cholesterol (35,36). Because the ratio of self-reported circumference measures will have more error than weight and height, the RRs for circumferences will tend to be underestimated to a greater degree than the RRs for BMI.

In this study, self-reported diabetes was confirmed by a supplementary questionnaire. However, because we did not screen our population, 3–9% of the men may have undiagnosed NIDDM (37). Although, in this cohort, 78% of the men had seen their physician for routine physicals within the first 2 years of follow-up. Underdiagnosis would have little effect on the RRs as long as the subset of undiagnosed cases did not differ greatly from the rest of the cases by levels of BMI. Among only symptomatic cases, the RRs of diabetes associated with levels of BMI were not substantively different from the risks found among the complete case population. Thus, underdiagnosis of asymptomatic cases is not likely to have significantly influenced the observed association between obesity and risk of diabetes. Furthermore, when we removed the cases diagnosed in the first 2 years of follow-up, the results were not appreciably different from those presented. Among the 194 cases diagnosed between 1989 and 1992, men with a BMI ≥35 kg/m$^2$ had a multivariate RR of diabetes of 53.9 (95% CI 24.3–119.5).

As indicated in Table 2 and Fig. 1, early obesity strongly predicts the risk of diabetes. Even men with a BMI between 23.0 and 24.9 kg/m$^2$ at age 21 had an increased risk after controlling for age, smoking, family history, and weight gain since age 21.

Similarly, overall absolute weight gain throughout adulthood was strongly related to risk of diabetes, regardless of BMI at age 21. Clearly, those who began with a higher BMI (≥24 kg/m$^2$) and gained substantial weight, (≥11.0 kg) had the highest RR (RR = 21.1, 95% CI 8.5–52.3). However, the steady increase along both axes shows that almost any weight gained after adolescence is associated with a higher risk of diabetes. We observed similar results in women in the Nurses' Health Study (1). These data suggest that it may be equally important to attain a healthy weight earlier in life as well as maintain it throughout adulthood.

Prior study of this cohort showed that BMI increased with age up to ages 60–65 and then decreased while average waist circumference increased continuously across all age-groups (38). This suggests a natural increase in adiposity with aging, as indicated by the increasing waist circumferences accompanied by a decrease in lean body mass after age 65. Other longitudinal studies have found that after age 65, men experience rapid loss of lean body mass (39,40). Age-related changes in body mass composition may make BMI a less appropriate indicator of total obesity in older subjects and could explain the observed reduction in magnitude of the risk of diabetes associated with BMI after age 60 (Table 5).

The data from this investigation imply that fat distribution, as measured by WHR, may contribute to one's risk of

diabetes when analyzed separately from other factors. However, after controlling for relative weight, WHR was only a significant risk factor for diabetes and then weakly among men in the top 5% with a WHR >1.03.

Fat distribution has predicted diabetes in several other studies. Although this association has been more pronounced in women (2), a few studies have emphasized the parallel importance in men. Haffner et al. (7) found that WHR was a better single screening measure for NIDDM than BMI and that upper body adiposity predicted diabetes even in lean men and women. Ohlson et al. (8) also found that WHR was positively and significantly associated with NIDDM even after BMI was considered among men in the top two tertiles of the study. This was a 13.5-year prospective study of 792 54-year-old men in Göteborg, Sweden; however, there were only 37 cases of diabetes confirmed at the time of analysis (6). Cassano et al. (3) observed a 2.4 times greater risk (95% CI 1.7–3.7) for men in the top tertile for the ratio of abdominal circumference to hip breadth compared with men in the lowest tertile, after controlling for BMI, cigarette smoking, and age after 18 years of follow-up. These studies controlled for BMI in either quintile or tertile groups. Hence, the stronger observed associations between WHR and diabetes risk may well be due to inadequate control of BMI; the current study controlled for BMI in nine categories.

Waist circumference (both height-adjusted and crude) was positively associated with the risk of diabetes within each quartile group of the top 20% of waist circumference, and the magnitude of excess risk was stronger than with WHR after controlling for relative weight, height, smoking, family history, and age. Adjusting waist for height did not appreciably influence the magnitude of association with diabetes risk; because simple waist measurements are easy to make, this may have practical importance in clinical settings. The increased risks of diabetes associated with having a high WHR and the increased risks observed among men with large waist circumferences may both be due to the metabolic complications of having high levels of abdominal adiposity. Because waist circumference has less measurement error than WHR, it may be a better indicator of the relationship between abdominal adiposity and the risk of diabetes.

Further follow-up of the Health Professionals cohort would be necessary to substantiate the current findings. It is possible that as the cohort ages, some measure of abdominal adiposity may emerge as an independently important risk factor for diabetes among leaner men. Metabolic data suggest that abdominal adiposity is associated with elevated plasma levels of free fatty acids, insulin insensitivity, and impaired glucose tolerance (19,21,25–27).

The results of this investigation show that current BMI, early obesity, absolute weight gain throughout adulthood, and abdominal adiposity measured by waist circumference are important independent risk factors for diabetes. Family history and age are accepted risk factors for diabetes (1,11,41), but only weight change is controllable. For incident diabetes, the hypothesized importance of weight distribution over general body size may be overemphasized. Fat distribution appears to be a modest independent risk factor for diabetes among men in the top 5% of WHR, but the strong RRs associated with even moderate BMI levels suggest that overall obesity is the dominant risk factor for diabetes. Thus, public health recommendations should primarily emphasize the prevention of overall obesity to reduce the occurrence of NIDDM. Ideally, a lean weight should be attained early in life and maintained throughout adulthood.

**Acknowledgments**— This study was supported by research grants HL-35464 and CA-55075 from the National Institutes of Health and P30-DK-46200 from the Boston Obesity/Nutrition Research Center.

**References**

1. Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE: Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 132:501–513, 1990
2. Hartz AJ, Rupley DC, and Rimm AA: The association of girth measurements with disease in 32,856 women. *Am J Epidemiol* 119:71–80, 1984
3. Cassano PA, Rosner B, Vokonas PS, Weiss ST: Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 136:1474–1486, 1992
4. Barrett-Connor E: Epidemiology, obesity, and non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:172–180, 1989
5. Seidell JC, Bakx JC, De Boer E, Deurenberg P, Hautvast JGAJ: Fat distribution of overweight persons in relation to morbidity and subjective health. *Int J Obes* 9:363–374, 1985
6. Ohlson LO, Larsson B, Björntorp P, Eriksson J, Svardsudd K, Welin L, Tibblin G, Wilhelmsen L: Risk factors for type 2 (non-insulin-dependent) diabetes mellitus: thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 31:798–805, 1988
7. Haffner SM, Mitchell BD, Stern MP, Hazuda HP, Patterson JK: Public health significance of upper body adiposity for non-insulin- dependent diabetes mellitus in Mexican Americans. *Int J Obes* 16:177–84, 1992
8. Ohlson LO, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G: The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 34:1055–1058, 1985
9. Fujimoto WY, Leonetti DL, Bergstrom RW, Shuman WP, Wahl PW: Cigarette smoking, adiposity, non-insulin-dependent diabetes, and coronary heart disease in Japanese-American men. *Am J Med* 89: 761–771, 1990
10. Charles MA, Fontbonne A, Thibult N, Warnet JM, Rosselin GE, Eschwege E: Risk factors for NIDDM in white popula-

tion: Paris prospective study. *Diabetes* 40: 96–99, 1991
11. Mykkänen L, Laakso M, Uusitupa M, Pyorala K: Prevalence of diabetes and impaired glucose tolerance in elderly subjects and their association with obesity and family history of diabetes. *Diabetes Care* 13:1099–1105, 1990
12. Dowse GK, Zimmet PZ, Gareeboo H, Alberti K, Tuomilehto J, Finch CF, Chitson P, Tulsidas H: Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. *Diabetes Care* 14:271–282, 1991
13. Kaye SA, Folsom AR, Sprafka JM, Prineas RJ, Wallace RB: Increased incidence of diabetes mellitus in relation to abdominal adiposity in older women. *J Clin Epidemiol* 44:329–334, 1991
14. Stern MP, Gonzalez C, Mitchell BD, Villalpando E, Haffner SM, Hazuda HP: Genetic and environmental determinants of type II diabetes in Mexico City and San Antonio. *Diabetes* 41:484–492, 1992
15. O'Dea K, White NG, and Sinclair AJ: An investigation of nutrition-related risk factors in an isolated Aboriginal community in Northern Australia: advantages of a traditionally orientated life-style. *Med J Aust* 148:177–180, 1988
16. Knowler WC, Pettitt DJ, Saad MF, Charles MA, Nelson RG, Howard BV, Bogardus C, Bennett PH: Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr* 53:1543S–1551S, 1991
17. Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE: Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 55:1018–1023, 1992
18. Pi-Sunyer FX: Health implications of obesity. *Am J Clin Nutr* 53:1595S–1603S, 1991
19. Fujioka S, Matsuzawa Y, Tokunaga K, Kawamoto T, Kobatake T, Keno Y, Kotani K, Yoshida S, Tarui S: Improvement of glucose and lipid metabolism associated with selective reduction of intra-abdominal visceral fat in premenopausal women with visceral fat obesity. *Int J Obes* 15: 853–859, 1991
20. Deibert DC, and DeFronzo RA: Epinephrine-induced insulin resistance in men. *J Clin Invest* 65:717–721, 1980
21. Schutz Y and Tremblay A: Does lipid oxidation differ in gynoid and android obese women? *Int J Obes* 16:67–69, 1992
22. Olefsky JM: Insulin resistance and insulin action in vitro and in vivo perspective. *Diabetes* 30:148–162, 1981
23. Pedersen O, Hjollund E, Sorensen HS: Insulin receptor binding and insulin action in human fat cells, effects of obesity and fasting. *Metabolism* 31:884–895, 1982
24. Beck-Nielson H, Pederson O, Lindkov HO: Normalization of insulin sensitivity and the cellular insulin binding during treatment of diabetics for one year. *Acta Endocrinol* 90:103–112, 1979
25. Kather M, Schröder F, Simon B, Schlierf G: Human fat cell adenylate cyclase: regional differences in hormone sensitivity. *Eur J Clin Invest* 7:595–597, 1977
26. Smith U, Hammarsten J, Björntorp P, Kral JG: Regional differences and effect of weight reduction of human fat cell metabolism. *Eur J Clin Invest* 9:327–332, 1979
27. Després J, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C: Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis* 10:497–511, 1990
28. Rimm EB, Giovannucci EL, Willett WC: Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* 338:464–468, 1991
29. Rimm EB, Stampfer MJ, Colditz GA, Giovannucci E, Willett WC: Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. *Am J Epidemiol* 131:1068–1071, 1990
30. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC: Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1:466–473, 1990
31. Rhoads GG, Kagan A: The relation of coronary disease, stroke, and mortality to weight in youth and in middle age. *Lancet* 1:492–495, 1983
32. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
33. Kleinbaum DG, Kupper LL, Morganstern H: *Epidemiologic Research: Principles and Quantitative Methods*. New York, Van Norstrand Reinhold, 1982, p. 140–150, 320–376
34. Spiegelman D, Israel RG, Bouchard C, Willett WC: Absolute fat mass, percent body fat, and body-fat distribution: which is the real determinant of blood pressure and serum glucose? *Am J Clin Nutr* 55: 1033–1044, 1992
35. Rosner B, Hennekens C, Kass EH, Miall WE. Age specific correlations analysis of longitudinal blood pressure data. *Am J Epidemiol* 106:306–313, 1977
36. Shekelle RB, Shryrock AM, Paul O: Diet, serum cholesterol, and death from coronary heart disease. *N Engl J Med* 304:65–70, 1981
37. Harris MI: Prevalence of non-insulin-dependent diabetes and impaired glucose tolerance. In *Diabetes in America: Diabetes Data*. Vol. 6. National Diabetes Data Group, Eds. Bethesda, MD, National Institutes of Health, 1985, p. 1–32 (DHHS publ. no. PHS 85–1468)
38. Giovannucci E, Rimm EB, Chute CC, Kawachi I, Colditz GA, Stampfer MJ, Willitt WC: Obesity and benign prostatic hyperlasia: a prospective study. *Am J Epidemiol*. In press
39. Borkan GA, Norris AG: Fat redistribution and the changing body dimensions of the adult male. *Hum Biol* 49:495–514, 1977
40. Flynn MA, Nolph GB, Baker AS, Martin WM, Krause G: Total body potassium in aging humans: a longitudinal study. *Am J Clin Nutr* 50:713–717, 1989
41. Fujimoto WY, Leonetti DL, Newell-Morris L, Shuman WP, Wahl PW: Relationship of absence or presence of a family history of diabetes to body weight and body fat distribution in type 2 diabetes. *Int J Obes* 15:111–120, 1991