Changes in Body Weight and Body Fat Distribution as Risk Factors for Clinical Diabetes in US Men

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Although previous studies have linked obesity to diabetes, the risks associated with weight gain or changes in body fat distribution have not been fully elucidated. The authors therefore prospectively examined the relations between changes in body weight and body fat distribution (1986–1996) and the subsequent risk of diabetes (1996–2000) among 22,171 men in the Health Professionals Follow-up Study. Weight gain was monotonically related to risk, and for every kilogram of weight gained, risk increased by 7.3%. A gain in abdominal fat was positively associated with risk, independent of the risk associated with weight change. Compared with men who had a stable waist, men who increased waist circumference by 14.6 cm or more had 1.7 (95% confidence interval: 1.0, 2.8) times the risk of diabetes after controlling for weight gain. In contrast, men who lost more than 4.1 cm in hip girth had 1.5 (95% confidence interval: 1.0, 2.3) times the risk of diabetes compared with men with stable hip circumference. Fifty-six percent of the cases of diabetes in this cohort could be attributed to weight gain greater than 7 kg, and 20 percent of the cases could be attributed to a waist gain exceeding 2.5 cm. Our findings underscore the critical importance of maintaining weight and waist to reduce the risk of diabetes.

adipose tissue; aging; body composition; diabetes mellitus, type II; hip; obesity

Abbreviations: CI, confidence interval; SD, standard deviation.

The dramatic rise in obesity in Westernized countries is alarming and has already contributed to substantial increases in cardiovascular disease, type 2 diabetes, hypertension, hypercholesterolemia, and certain cancers (1–12). Although previous studies have closely linked obesity to the development of diabetes (1, 3, 4, 7, 9, 13), the risks associated with weight gain or changes in body fat distribution have not been fully elucidated. Whether changes in the localization of body fat affect the risk of diabetes independent of changes in total body weight remains unknown, and the magnitude by which these risks may compare with changes in overall obesity deserves further exploration. For these reasons, we prospectively examined the relations between changes in body weight and body fat distribution and the subsequent risk of

diabetes in a large population of US men. We previously reported the associations between baseline body mass index, weight gain, and body fat distribution and clinical diabetes in this cohort (6).

MATERIALS AND METHODS

Study population

The Health Professionals Follow-up Study is a prospective investigation of 51,529 male health professionals aged 40–75 years at baseline in 1986. In 1986, participants completed a detailed questionnaire and reported their current height and weight, medical history, heart disease risk factors, and

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weight at age 21 years. On a biennial basis thereafter, participants were mailed questionnaires to update information on exposures and to ascertain newly diagnosed diseases, including type 2 diabetes.

Exposure assessment

In 1987, we sent out a brief follow-up questionnaire to obtain the participants' family history of diabetes. In addition, in 1987 and 1996, we included paper tape measures to assist the men in self-reporting their waist and hip circumferences. Men were asked to take measurements under bulky clothing and while standing. 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 our typical extensive follow-up procedures to increase our follow-up rate of greater than 65 percent (10). Thus, 17,427 men were excluded who had missing waist information in either 1987 or 1996. We further excluded 11,931 men who developed heart disease or cancer before 1986 or diabetes before 1996 or who died before 1996. Our analysis is therefore restricted to 22,171 men for whom we had a complete set of predictor information (1986–1996) before the period of incident diabetes ascertainment (1996 to 2000).

We assessed the validity of the self-reported anthropometric measurements in a random sample of 123 men living in the Boston, Massachusetts, area. We compared the self-reported weight, waist, and hip measurements with the mean of two technician-assessed measurements spaced approximately 6 months apart (14). After adjusting for age and within-person variability, we determined the correlation coefficients between the self-reported and technician-measured assessments to be 0.97 for weight, 0.95 for waist, 0.88 for hips, and 0.68 for the waist/hip ratio. There were no significant linear trends in the accuracy of reported waist circumference across quartiles of either age or body mass index (14). 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 ($r = 0.83$) (15). We calculated the participants' change in body weight (in kilograms) between the age of 21 years and 1996 and also between 1986 and 1996. Changes in waist circumference, waist/hip ratio, and hip girth were calculated between 1987 and 1996. Exposure information on potential confounders, including diet and physical activity (16, 17), was obtained from the baseline 1986 and follow-up questionnaires.

Case ascertainment

The endpoints for type 2 diabetes case ascertainment were the return of the 1996 questionnaire and January 31, 2000. We excluded men who reported diabetes before January 1, 1996. A diagnosis of diabetes was confirmed from a supplementary questionnaire sent to participants who indicated a new diagnosis of diabetes on a biennial questionnaire. We confirmed a diagnosis of incident diabetes if the participant met one of the following criteria: 1) manifestation of one or more classic symptoms (thirst, polyuria, weight loss, hunger, or pruritus), plus a fasting plasma glucose level of at least 140 mg/dl or a random plasma glucose level of at least 200 mg/dl; or 2) at least two elevated plasma glucose concentrations on different occasions (fasting level of at least 140 mg/dl and/or random level of at least 200 mg/dl and/or concentration of at least 200 mg/dl after ≥2 hours of oral glucose tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). Our criteria were in accordance with those of the National Diabetes Data Group during this time period except that we did not use any weight criteria in classifying diabetes (18). We did not screen for undiagnosed cases of diabetes in this population.

To examine the validity of self-reported diabetes, we obtained medical records from 71 men, selected at random, who reported diabetes and were classified as having definite type 2 diabetes by the supplementary questionnaire. A physician blinded to the information reported on the questionnaire reviewed the records according to the diagnostic criteria. Although 12 of the 71 men had incomplete records, each of these cases was strongly suggestive of diabetes. Among the remaining 59 cases, the diagnosis of diabetes was confirmed in 57 subjects (97 percent) (19).

Statistical analysis

Men were classified according to the following changes: 1) their long-term change in weight from 21 years of age to 1996; 2) their recent weight change from 1986 to 1996; and 3) their changes in waist, waist/hip ratio, and hip circumference from 1987 to 1996. Correlation analysis was used to assess the relation between the various outcome measures. We used Cox proportional hazards models to analyze the associations between the various anthropometric measures, as categorical and continuous variables, and type 2 diabetes (20). We used left-truncated Cox models in all analyses, with age (months) by calendar year/questionnaire cycle as the time scale. Each participant contributed follow-up time from the return date of the 1996 questionnaire until the diagnosis of diabetes, death from other causes, or January 31, 2000, whichever came first.

Incident rates were calculated by dividing the number of incident cases by the number of person-years of follow-up in each category of change in body weight or fat distribution. We then calculated the crude hazard ratio and the 95 percent confidence interval as a measure of the relative risk for type 2 diabetes, computed as the rate of diabetes for a specific category divided by the rate of the reference category. The reference category was selected to reflect a stable weight (±2 kg), and the remaining range of weight change was divided into five categories with whole number cutoff points. Tests of linear trend were conducted by assigning the median measure for the category and fitting the new variable as continuous in the model. The multiple regression models controlled for family history of diabetes, smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (g/day), dietary fiber (g/day), physical activity (metabolic equivalent-hours/week), and the appropriate baseline anthropometric measure.

TABLE 1. Relative risk and 95% confidence interval for diabetes (1996–2000) by body mass index at age 21 years and weight change from 21 years of age to 1996 among US men in the Health Professionals Follow-up Study

Range	Person-years of follow-up	No. of cases	Relative risk			
			Adjusted for age		Multivariate adjusted	
			RR*	95% CI*	RR	95% CI
Body mass index at age 21 years (kg/m²)†						
<21.0	19,033	66	1.0		1.0	
21.0–22.9	24,407	67	0.8	0.6, 1.1	1.2	0.8, 1.6
23.0–24.9	21,968	72	1.0	0.7, 1.3	1.5	1.1, 2.2
25.0–29.9	15,668	90	1.7	1.2, 2.3	2.6	1.9, 3.6
≥30.0	1,012	10	2.9	1.5, 5.7	4.9	2.5, 9.7
Weight change from age 21 years to 1996 (kg)‡						
Loss of ≥3	8,299	7	0.6	0.3, 1.5	0.4	0.2, 1.1
Loss of 2–gain of 2	12,334	17	1.0		1.0	
Gain of 3–6	16,632	40	1.7	1.0, 3.0	1.8	1.0, 3.2
Gain of 7–11	17,742	48	1.9	1.1, 3.4	2.1	1.2, 3.6
Gain of 12–18	15,926	61	2.7	1.6, 4.7	3.0	1.8, 5.2
Gain of ≥19	11,157	132	8.5	5.1, 14.0	8.8	5.2, 14.7

* RR, relative risk; CI, confidence interval.

† Analysis includes 22,171 participants (305 cases) with complete information on body mass index at age 21 years. Multivariate relative risk model for body mass index at age 21 years controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (six categories), physical activity (quintiles), family history of diabetes, dietary fiber (quintiles), and weight change since age 21 years (continuous).

‡ Multivariate relative risk model for weight change since age 21 years controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (six categories), physical activity (quintiles), family history of diabetes, dietary fiber (quintiles), and body mass index at age 21 years (continuous).

The covariates were included as linear terms when tests for nonlinearity using spline regression were not statistically significant on the log scale; otherwise, the exposures were categorized.

Joint associations of body mass index in young adulthood and long-term weight gain with risk of diabetes were modeled by jointly classifying men by relative weight at age 21 years and categories of weight gain from age 21 years to 1996.

We further examined the relation of changes in weight and body fat distribution with the incidence of diabetes by level of family history of diabetes.

We calculated the population attributable risks (21, 22), estimates of the percentage of cases of type 2 diabetes in this population that would theoretically not have occurred, if all men had gained less than the median values for the respective exposure measures among men in the cohort, namely: 1) long-term weight gain of 7 or more kg and 2) 9-year waist gain of 2.5 or more cm, assuming a causal relation between the risk factor and type 2 diabetes. All *p* values were two sided, and statistical analyses were conducted using SAS version 8.2 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

In 1986, men were 40–75 years of age, with a mean age of 53.3 (standard deviation (SD), 9.4) years. Between 1996 and 2000, we documented 305 new incident cases of diabetes. The mean body weight at age 21 years in this cohort was 72.9 (SD, 10.0) kg, while the mean change in weight from age 21 years to 1996 was 9.0 (SD, 9.5) kg. Long-term weight gain was strongly related to the risk of diabetes in a monotonic fashion (table 1). Compared with men whose weight remained stable (±2 kg), men who gained 3–6 kg throughout adulthood had 1.8 times the risk for diabetes (95 percent confidence interval (CI): 1.0, 3.2) after controlling for family history, smoking, alcohol, dietary fiber, physical activity, and body mass index at age 21 years. Men who gained 7–11 kg had an increased risk of 2.1 (95 percent CI: 1.2, 3.6), while those who gained 12–18 kg had a relative risk of 3.0 (95 percent CI: 1.8, 5.2). Men who experienced the highest degree of weight gain (≥19 kg) had a risk 8.8 (95 percent CI: 5.2, 14.7) times greater than those men whose weight remained stable. When change in weight was considered as a continuous variable, the multivariate relative risk for diabetes increased by 7.3 (95 percent CI: 6.2, 8.4) percent for each kilogram of weight gain. The number of men who lost substantial weight after 21 years of age was few, and the multivariate relative risk for weight loss of 3 kg or more during this period was 0.4 (95 percent CI: 0.2, 1.1).

We also examined the joint association of long-term weight change (from age 21 years to 1996) and early adiposity (body mass index at age 21 years) with risk of
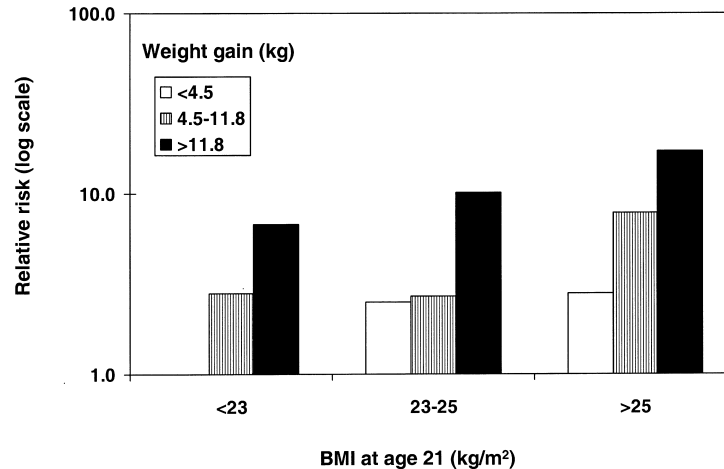
FIGURE 1. Multivariate relative risk for diabetes (1996–2000) by level of body mass index (BMI) at age 21 years and weight gain from 21 years of age to 1996 among US men in the Health Professionals Follow-up Study. Multivariate relative risk controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol intake (six categories), physical activity (quintiles), family history of diabetes, and dietary fiber (quintiles). Men with a body mass index of less than 23 at age 21 years and with stable weight (<4.5-kg gain from age 21 years to 1996) were the reference category.

diabetes. Weight gain across all levels of body mass index at age 21 years was significantly related to the risk of diabetes in multivariate analyses. The risk for diabetes increased within each tertile of weight gain as well as within each category of body mass index at age 21 years (figure 1).

Recent weight gain and type 2 diabetes

In 1996, the mean body weight was 82.0 (SD, 12.1) kg. The mean weight change from 1986 to 1996 was 1.8 (SD, 5.2) kg. Compared with men having stable weight, men who lost the most weight over this 10-year period (≥6 kg) had a 50 (95 percent CI: 10, 70) percent reduction in risk after controlling for family history, smoking, alcohol, dietary fiber, physical activity, and relative body weight in 1986 (table 2). In contrast, men who gained 3–5 kg had 1.4 times the risk of diabetes (95 percent CI: 1.0, 1.9). The relative risks for diabetes among men were 1.6 (95 percent CI: 1.1, 2.4) and 2.1 (95 percent CI: 1.5, 3.0) for men who gained 6–8 kg and 9 kg or more, respectively, between 1986 and 1996.

Changes in waist, waist/hip ratio, and hip circumference and type 2 diabetes

The correlation of 0.51 between changes in body weight and waist was modest in comparison with the correlation between body mass index and waist at baseline ($r = 0.77$). These findings reflect how changes in body weight alone may not adequately capture alterations in insulin resistance among men in their sixties and seventies when losses in lean muscle mass occur concomitantly with increases in adiposity (23, 24). Therefore, we examined changes in body fat distribution and the subsequent risk of diabetes (table 3). The mean 9-year changes were 3.1 (SD, 5.6) cm for waist

circumference, 0.02 (SD, 0.05) for waist/hip ratio, and 1.5 (SD, 5.0) cm for hip girth. We categorized the changes in waist circumference, waist/hip ratio, and hip girth into five groups and calculated the hazard ratios using three different models: 1) controlling for age only; 2) controlling for family history, smoking, alcohol, dietary fiber, physical activity, body mass index in 1986, and the respective baseline anthropometric measure in 1987; and 3) additionally controlling for the change in body weight between 1986 and 1996.

In multivariate analyses, men who lost more than 2.6 cm of waist girth had a relative risk of 0.8 (95 percent CI: 0.5, 1.1) compared with men whose waist remained stable (±2.5 cm). In contrast, men whose waist increased by 2.6–6.4 cm had a multivariate relative risk of 1.3 (95 percent CI: 1.0, 1.7). Men who experienced the most waist gain (≥14.6 cm) had 2.4 (95 percent CI: 1.5, 3.7) times the risk of diabetes in multivariate analyses. After simultaneously controlling for weight change during this same period, we found all relative risks to be attenuated, and only waist gain in the highest category was significantly related to diabetes risk (relative risk for highest quintile of change = 1.7, 95 percent CI: 1.0, 2.8).

Although the waist circumference may better reflect the increase in visceral fat than the waist/hip ratio (25, 26), we further examined the association for changes in waist/hip ratio, since the waist/hip ratio is a robust measure of risk in many population studies (27). Importantly, the predictive value of the waist/hip ratio may not be solely due to increased abdominal fat, as assessed by waist circumference, but also due to a relative lack of peripheral muscle mass, as indicated by hip circumference (27–29). In our study, increases in waist/hip ratio were positively related to risk of diabetes independent of weight gain. The multivariate relative risks for progressive increases in waist/hip ratio were 1.7 (95 percent CI: 1.2, 2.4), 1.5 (95 percent CI: 1.0, 2.4), and

TABLE 2. Relative risk and 95% confidence interval for diabetes (1996–2000) by body mass index in 1986 and 10-year weight change from 1986 to 1996 among US men in the Health Professionals Follow-up Study

Range	Person-years of follow-up	No. of cases	Relative risk					
			Adjusted for age		Multivariate adjusted		Multivariate adjusted*	
			RR†	95% CI†	RR	95% CI	RR	95% CI
Body mass index in 1986 (kg/m²)‡								
<23.0	16,943	18	1.0		1.0		1.0	
23.0–24.9	25,141	55	2.1	1.2, 3.5	2.0	1.2, 3.5	1.9	1.1, 3.2
25.0–26.9	22,039	81	3.4	2.0, 5.7	3.1	1.9, 5.3	2.7	1.6, 4.5
27.0–29.9	13,316	80	5.6	3.4, 9.4	5.0	3.0, 8.3	3.9	2.3, 6.5
≥30.0	4,655	71	14.1	8.4, 23.7	10.8	6.4, 18.3	7.6	4.4, 13.1
Weight change from 1986 to 1996 (kg)§								
Loss of ≥6	5,198	13	0.9	0.5, 1.6	0.5	0.3, 0.9	0.5	0.3, 0.9
Loss of 3–5	10,493	34	1.2	0.8, 1.7	1.0	0.7, 1.5	1.0	0.7, 1.5
Loss of 2–gain of 2	36,189	99	1.0		1.0		1.0	
Gain of 3–5	16,187	64	1.5	1.1, 2.1	1.4	1.0, 1.9	1.3	1.0, 1.9
Gain of 6–8	6,779	34	2.0	1.3, 2.9	1.6	1.1, 2.4	1.5	1.0, 2.3
Gain of ≥9	7,242	61	3.4	2.4, 4.7	2.1	1.5, 3.0	1.9	1.4, 2.7

* Multivariate relative risk model additionally controls for waist/hip ratio in 1987 (continuous) and change from 1987 to 1996 in waist/hip ratio (continuous).

† RR, relative risk; CI, confidence interval.

‡ Analysis includes 22,171 participants (305 cases) with complete information on body mass index in 1986. Multivariate relative risk model for body mass index in 1986 controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (six categories), physical activity (quintiles), family history of diabetes, dietary fiber (quintiles), and weight change since 1986 (continuous).

§ Multivariate relative risk model for 10-year weight change controls for smoking status, alcohol, physical activity, family history, dietary fiber, and body mass index in 1986 (continuous).

2.2 (95 percent CI: 1.3, 3.7) in comparison with stable waist/hip ratio (±0.01).

Decreases in hip girth were significantly associated with diabetes risk in multivariate analyses that controlled for concurrent weight change. Compared with men who had a stable hip circumference, men who lost more than 4.1 cm in hip circumference had 1.5 times the risk of diabetes (95 percent CI: 1.0, 2.3).

Subgroup analyses

To explore the possibility that the relation between weight gain and the risk of diabetes differed among the participants excluded as a result of missing anthropometric measures, we calculated the multivariate relative risk for weight gain limited to those men with only missing waist or hip circumference measurements. Among this subset, the risk for diabetes associated with the various categories of long-term weight gain was very similar to that of the original population for analysis.

Since the development of coronary heart disease and cancer may lead to changes in weight and risk of diabetes, we reanalyzed the data and controlled for the development of these diseases through 1996. The results were not appreciably different from those presented above.

The associations between weight gain, changes in waist/hip ratio, and hip girth and risk of diabetes were not materi-

ally modified by family history of diabetes (figure 2). Although the test of interaction was not statistically significant, among men with a family history, waist gain exceeding 14.6 cm was associated with 2.7 (95 percent CI: 1.2, 5.9) times the risk of diabetes in comparison with those having a stable waist after controlling for concurrent weight change. In contrast, the highest quintile of waist gain for men without a family history did not significantly increase risk (relative risk = 1.3, 95 percent CI: 0.7, 2.5).

Population attributable risks

Finally, because body weight is such an important predictor of diabetes and weight gain is so ubiquitous, we calculated the population attributable risk of diabetes associated with our prospective measures of change (21, 22), controlling for smoking status, alcohol consumption, physical activity, family history of diabetes, dietary fiber, and the respective baseline anthropometric measure. Of the new cases of diabetes in this cohort, 56 (95 percent CI: 45, 65) percent could be attributed to long-term weight gain greater than 7 kg (table 4); 20 (95 percent CI: 7, 32) percent of cases could have been prevented if the increase in waist circumference did not exceed 2.5 cm. The percentages of cases attributed to weight and waist gain were not mutually exclusive, since the analysis for waist gain did not control for concurrent weight change.

TABLE 3. Change in waist, waist/hip ratio, and hips from 1987 to 1996 as risk factors for diabetes (1996–2000) among US men in the Health Professionals Follow-up Study

	Relative risk by quintile of change										
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5		p_{trend}
	RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	
Waist change from 1987 to 1996											
Range (cm)	Loss of ≥2.6		Loss of 2.5–gain of 2.5		Gain of 2.6–6.4		Gain of 6.5–14.5		Gain of ≥14.6		
Cases (no.)	44		91		85		61		24		
Adjusted for age	1.2	0.8, 1.7	1.0		1.4	1.0, 1.8	1.3	0.9, 1.8	3.0	1.9, 4.7	0.002
Multivariate adjusted†	0.8	0.5, 1.1	1.0		1.3	1.0, 1.7	1.0	0.8, 1.5	2.4	1.5, 3.7	0.001
Multivariate adjusted‡	0.9	0.6, 1.3	1.0		1.2	0.8, 1.6	0.8	0.6, 1.2	1.7	1.0, 2.8	0.5
Waist/hip ratio change from 1987 to 1996											
Range	Loss of ≥0.02		Loss of 0.01–gain of 0.01		Gain of 0.02–0.05		Gain of 0.06–0.09		Gain of ≥0.1		
Cases (no.)	92		41		107		40		25		
Adjusted for age	1.5	1.0, 2.2	1.0		1.7	1.2, 2.4	1.7	1.1, 2.6	2.4	1.5, 4.0	0.03
Multivariate adjusted†	1.2	0.8, 1.7	1.0		1.8	1.2, 2.5	1.7	1.1, 2.7	2.5	1.5, 4.1	<0.001
Multivariate adjusted‡	1.2	0.8, 1.7	1.0		1.7	1.2, 2.4	1.5	1.0, 2.4	2.2	1.3, 3.7	0.003
Hip change from 1987 to 1996											
Range (cm)	Loss of ≥4.1		Loss of 1.4–4.0		Loss of 1.3–gain of 1.3		Gain of 1.4–5.0		Gain of ≥5.1		
Cases (no.)	41		41		72		77		74		
Adjusted for age	1.7	1.1, 2.5	1.4	0.9, 2.0	1.0		1.0	0.8, 1.4	1.8	1.3, 2.5	0.4
Multivariate adjusted†	1.2	0.8, 1.8	1.3	0.9, 1.9	1.0		1.0	0.7, 1.4	1.4	1.0, 2.0	0.5
Multivariate adjusted‡	1.5	1.0, 2.3	1.4	0.9, 2.1	1.0		0.9	0.6, 1.2	1.0	0.7, 1.5	0.05

* RR, relative risk; CI, confidence interval.
† Multivariate relative risk model controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (six categories), physical activity (quintiles), family history of diabetes, dietary fiber (quintiles), body mass index in 1986 (continuous), and the respective baseline anthropometric measure in 1987 (continuous).
‡ Multivariate relative risk model additionally controls for change in weight between 1986 and 1996 (continuous).
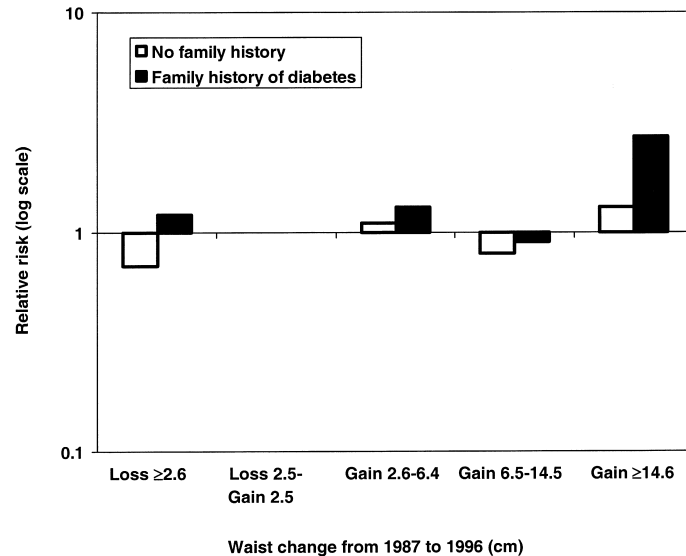
FIGURE 2. Multivariate relative risk for diabetes (1996–2000) by waist change from 1987 to 1996 and family history of diabetes among US men in the Health Professionals Follow-up Study. Multivariate relative risk model controls for waist in 1987 (continuous), body mass index in 1986 (continuous), smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol intake (six categories), physical activity (quintiles), dietary fiber (quintiles), and change in weight from 1986 to 1996 (continuous). Men with a stable waist (loss of 2.5–gain of 2.5 cm) from 1987 to 1996 were the reference category within each stratum of family history of diabetes.

DISCUSSION

Substantial, possibly diabetogenic changes in body composition related to fat and skeletal muscle mass occur with aging (27). In particular, peripheral muscle mass declines during aging, whereas abdominal fat continuously increases with age (30, 31). These changes are concordant with the observation that body mass index and hip circumference increase until the ages of 60–65 years and then decline among men, whereas waist circumference increases until very old age (32). Although such changes in the distribution of body weight may increase diabetes risk, few studies have assessed the potential risks because of the lack of repeated measures of weight, waist, and hip circumferences over time.

In our prospective analysis, we determined that changes in body weight and body fat distribution were significantly associated with the risk of diabetes. Weight gain was monotonically related to risk, and for every kilogram of weight gained, risk increased by 7.3 percent. The accumulation of abdominal fat, as assessed by increases in waist circumference and waist/hip ratio, was positively related to risk, independent of changes in body weight. In contrast, men who lost hip girth had a 50 percent increased risk of diabetes in multivariate analyses that controlled for concurrent weight change. To our knowledge, this is the first prospective cohort study to report the association between changes in body fat distribution and incident diabetes.

Previous studies have documented the hazardous effects of obesity on the risk of diabetes (1, 3, 4, 7, 9). In one nationally representative sample of US adults, the risk of diabetes increased 4.5 percent for every kilogram of increase in body weight, and this association was consistent across various levels of age, sex, and ethnicity (3). It is particularly salient to our the study that the risks of developing diabetes were reduced by approximately 50 percent as a result of weight loss exceeding 6 kg over a 10-year period. In this population, a 6-kg weight loss comprised approximately 7.5 percent of initial body weight. Our results are in accordance with the landmark findings of the Diabetes Prevention Project, in which intensive lifestyle intervention including a weight reduction of at least 7 percent of initial body weight reduced the incidence of diabetes by 58 percent compared with the placebo group (33). Importantly, the findings from the Diabetes Prevention Project and other clinical trials point to the feasibility of weight loss achieved through simple lifestyle modifications (33–35).

In the current study, an increase in abdominal adiposity, as measured by a gain in waist circumference or waist/hip ratio, was significantly related to risk of diabetes. Previously, baseline measures of waist girth and waist/hip ratio have been reported as moderate risk factors for type 2 diabetes (2, 6, 8, 36). After controlling for concurrent weight change, increases in waist/hip ratio remained consistently related to risk, while only the highest quintile of waist gain (≥14.6 cm) was related to risk. We do not know whether the only modest risk observed for gain in waist circumference may be attributed to low power. In this cohort, few men gained extensive waist in the absence of weight change. However, if abdominal obesity and peripheral muscle mass exert independent and opposite effects on diabetes, this may in part explain the consistent strength of association observed for the waist/hip

TABLE 4. Relative and population attributable risks for diabetes (1996–2000) according to the degree of weight and waist gain among US men in the Health Professionals Follow-up Study

Subgroup	% of men	No. of cases	RR*	95% CI*	PAR* (%)	95% CI
Weight gain of ≥7 kg since age 21 years†	55	241	3.3	2.5, 4.4	56	45, 65
Waist gain of ≥2.5 cm over 9 years‡	56	193	1.4	1.1, 1.8	20	7, 32

* RR, relative risk; CI, confidence interval; PAR, population attributable risk (percentage of type 2 diabetes cases in the population that would theoretically not have occurred if all men had gained less weight than the given cutpoints).

† Multivariate relative risk for weight gain controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (six categories), physical activity (quintiles), family history of diabetes, dietary fiber (quintiles), and body mass index at age 21 years (continuous).

‡ Multivariate relative risk for waist gain controls for smoking status (never smoked, formerly smoked, or currently smoking <15, 15–24, or ≥25 cigarettes/day), alcohol (six categories), physical activity (quintiles), family history of diabetes, dietary fiber (quintiles), body mass index in 1986 (continuous), and baseline waist in 1987 (continuous).

ratio versus the waist circumference, since the waist/hip ratio provides information on both aspects of change. Future analyses with a greater number of cases may provide a better understanding into the relative utility of these measures and the independent impact of waist gain.

In the current study, loss of hip girth was marginally associated with an increased risk of diabetes. It is unclear whether our findings may be attributed to chance. In an earlier report among the Health Professionals Follow-up Study cohort, baseline hip circumference was not significantly related to the risk of diabetes (6). However, in the Hoorn Study, a prospective study among men and women, large hip girth was associated with a lower risk of type 2 diabetes independent of body mass index, age, and waist circumference (37). In the Monitoring Risk Factors and Health in the Netherlands (MORGEN) project, diabetic men had significantly smaller hips compared with nondiabetic men in cross-sectional analyses (29).

The disparity in findings may be attributed to the use of baseline hip circumference. It is difficult to discern the amounts of fat mass, lean muscle, and skeletal frame in circumference measures (29, 38). However, a decrease in hip girth may primarily reflect a loss of lean tissue, particularly among men (23, 24). Studies have further linked the wasting of leg muscle mass with an increased risk of both diabetes and cardiovascular disease (28). Chowdhury et al. (28) reported that the disparities in glucose levels between Indian and Swedish men of similar age and body mass index were associated with differences in lower leg muscle mass, not visceral fat. While the thigh circumference is less influenced by frame size than the hip circumference, thereby serving as a better marker of lean muscle tissue, the hip circumference was more strongly related to glucose concentrations among men (37).

Narrow hip girth may be related to low muscle lipoprotein lipase activity with a concomitant reduction in the capacity of muscle to use fatty acids (27). Since skeletal muscle is the main target organ and site of insulin resistance (29), peripheral muscle wasting may contribute to diminished insulin clearance from muscle (39). It has further been suggested that a loss of lean mass due to altered amino acid utilization results in the subsequent release of nitrogenous metabolites that may impair insulin action (40).

Laboratory studies are needed to partition the sources of variation in hip loss over time by directly measuring the girth components and linking reductions in muscle mass to impairments in insulin sensitivity. Whether the underling etiologic mechanisms or consequences of hip loss are the same for women or diverse ethnic groups is intriguing and deserves further exploration.

Our prospective study design reduces the probability of biased reporting of weight and waist change after the diagnosis of diabetes. Because we did not screen our population, 3–9 percent of the men may have undiagnosed diabetes (41). However, it is unlikely that the diagnosis of diabetes is related to body weight, since we observed increasing relative risks for weight gain in each category of body mass index. Furthermore, more aggressive screening among heavier men likely did not bias our results as the prevalence of reported symptoms at diagnosis and the frequency of visits did not vary by body mass index (9).

As a limitation to the generalizability of our findings, this cohort consisted of middle- and older-aged men who were predominantly Caucasian. Given that the burden of diabetes falls disproportionately on ethnic minority groups in the United States (42), targeted interventions that account for the variation in lifestyle patterns associated with weight gain are necessary. Notably, clinical trials have demonstrated that modest weight loss, a low-fat diet, and increased physical activity significantly reduce the risk of progressing from impaired glucose tolerance to diabetes in men and women and among diverse racial groups (33–35).

The results of the present study show that an increase in abdominal adiposity and decrease in peripheral muscle mass may be important factors in the development of diabetes. Therefore, interventions aimed at the prevention of diabetes should combine approaches that alter weight and waist and hip circumferences (37). In a recent study among the same men, changes in several lifestyle factors were related to reductions in waist, independent of weight change, including decreased *trans*-fatty acid intake and television watching, increased fiber consumption, vigorous physical activity, and weight training (43). Furthermore, physical activity may expressly decrease abdominal fat while increasing lower muscle mass (44), in contrast to energy restriction that tends to decrease both waist and hip circumferences (37).

Because of the long delay between the onset of obesity and subsequent development of diabetes, the impact of the epidemic increase in obesity may not be realized for several years (45). Since even modest changes in weight and waist were associated with substantial increases in diabetes risk, our findings further underscore the importance of maintaining a constant body weight and waist throughout adulthood. The dual tasks of designing effective countermeasures against obesity and effectively communicating these practices to the public remain as major public health challenges.

REFERENCES

1. Hanson RL, Narayan KMV, McCance DR, et al. Rate of weight gain, weight fluctuation, and incidence of NIDDM. Diabetes 1995;43:261–6.
2. Carey VJ, Walters EE, Colditz GA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 1997;145:614–19.
3. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. Am J Epidemiol 1997;146:214–22.
4. Wannamethee GS, Shaper AG. Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. Diabetes Care 1999;22:1266–72.
5. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women: risk within the 'normal' weight range. JAMA 1995;273:461–5.
6. Chan JM, Rimm EB, Colditz GA, et al. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–9.
7. Holbrook TL, Barrett Connor E, Wingard DL. The association of lifetime weight and weight control patterns with diabetes among men and women in an adult community. Int J Obes 1989;13:723–9.
8. Cassano PA, Rosner B, Vokonas PS, et al. Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. Am J Epidemiol 1992;136:1474–86.
9. Colditz GA, Willett WC, Rotnizky A, et al. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–6.
10. Rimm EB, Stampfer MJ, Giovannucci E, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 1995;141:1117–27.
11. Rexrode KM, Hennekens CH, Willett WC, et al. A prospective study of body mass index, weight change, and risk of stroke in women. JAMA 1997;277:1539–45.
12. Folsom AR, Stevens J, Schreiner PJ, et al. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and Whites. Am J Epidemiol 1998;148:1187–94.
13. Flegal KM, Carroll MD, Ogden C, et al. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288:1723–7.
14. Rimm EB, Stampfer MJ, Colditz GA, et al. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
15. Rhoads GG, Kagan A. The relation of coronary disease, stroke, and mortality to weight in youth and in middle age. Lancet 1983;1:492–5.
16. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
17. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81–6.
18. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–57.
19. Conigrave KM, Hu BF, Camargo CA Jr, et al. A prospective study of drinking patterns in relation to risk of type 2 diabetes among men. Diabetes 2001;50:2390–5.
20. Cox DR. Regression models and life tables (with discussion). J R Stat Soc (B) 1972;34:187–220.
21. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1998.
22. Wacholder S, Benichou J, Heineman EF, et al. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 1994;140:303–9.
23. Flynn MA, Nolph GB, Baker AS, et al. Total body potassium in aging humans: a longitudinal study. Am J Clin Nutr 1989;50:713–17.
24. Borkan GA, Norris AG. Fat redistribution and the changing body dimensions of the adult male. Hum Biol 1977;49:495–514.
25. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460–8.
26. van der Kooy K, Seidell JC. Techniques for the measurement of visceral fat: a practical guide. Int J Obes Relat Metab Disord 1993;17:187–96.
27. Seidell JC, Perusse L, Despres JP, et al. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. Am J Clin Nutr 2001;74:315–21.
28. Chowdhury B, Lantz H, Sjostrom L. Computed tomography-determined body composition in relation to cardiovascular risk factors in Indian and matched Swedish males. Metabolism 1996;45:634–44.
29. Seidell JC, Han TS, Feskens EJM, et al. Narrow hips and broad waist circumferences independently contribute to increased risk of non-insulin dependent diabetes mellitus. J Intern Med 1997;242:401–6.
30. Borkan GA, Hults DE, Gerzof SG, et al. Comparison of body composition in middle-aged and elderly males using computed tomography. Am J Phys Anthropol 1985;66:289–95.
31. Rice CL, Cunningham DA, Paterson DH, et al. Arm and leg composition determined by computed tomography in young and elderly men. Clin Physiol 1989;9:207–20.
32. Teh BH, Pan WH, Chen CJ. The reallocation of body fat toward the abdomen persists to very old age, while body mass index declines after middle age in Chinese. Int J Obes Relat Metab Disord 1996;20:683–7.
33. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in

the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.

34. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344: 1343–50.

35. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20: 537–44.

36. Lundgren H, Bengtsson C, Blohme G, et al. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. Int J Obes 1989;13:413–23.

37. Snijder MB, Dekker JM, Visser M, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. Am J Clin Nutr 2003;77:1192–7.

38. Molarius A, Seidell JC. Selection of anthropometric indicators for classification of abdominal fatness—a critical review. Int J Obes Relat Metab Disord 1998;22:719–27.

39. Yki-Jarvinen H, Koivisto VA, Karonen SL. Influence of body composition on insulin clearance. Clin Physiol 1985;5:45–52.

40. Stein TP, Schulter MD, Boden G. Development of insulin resistance by astronauts during spaceflight. Aviat Space Environ Med 1994;65:1091–6.

41. Harris MI. Prevalence of non-insulin dependent diabetes and impaired glucose tolerance. In: National Diabetes Data Group, eds. Diabetes in America: diabetes data. Vol 6. Bethesda, MD: National Institutes of Health, 1985:1–32. (DHHS publication no. (PHS) 85-1468).

42. Ludwig DS, Ebbeling CB, Pereira MA, et al. A physiological basis for disparities in diabetes and heart disease risk among racial and ethnic groups. J Nutr 2002;132:2492–3.

43. Koh-Banerjee P, Chu NF, Spiegelman D, et al. Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. Am J Clin Nutr 2003;78:719–27.

44. Han TS, Bijnen FC, Lean ME, et al. Separate associations of waist and hip circumference with lifestyle factors. Int J Epidemiol 1998;27:422–30.

45. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990–1998. Diabetes Care 2000;23:1278–83.