Weight Gain as a Risk Factor for Clinical Diabetes Mellitus in Women

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Weight Gain as a Risk Factor for Clinical Diabetes Mellitus in Women

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■ *Objective:* To examine the relation between adult weight change and the risk for clinical diabetes mellitus among middle-aged women.

■ *Design:* Prospective cohort study with follow-up from 1976 to 1990.

■ *Setting:* 11 U.S. states.

■ *Participants:* 114 281 female registered nurses aged 30 to 55 years who did not have diagnosed diabetes mellitus, coronary heart disease, stroke, or cancer in 1976.

■ *Outcome Measures:* Non–insulin-dependent diabetes mellitus.

■ *Results:* 2204 cases of diabetes were diagnosed during 1.49 million person-years of follow-up. After adjustment for age, body mass index was the dominant predictor of risk for diabetes mellitus. Risk increased with greater body mass index, and even women with average weight (body mass index, 24.0 kg/m^2) had an elevated risk. Compared with women with stable weight (those who gained or lost less than 5 kg between age 18 years and 1976) and after adjustment for age and body mass index at age 18 years, the relative risk for diabetes mellitus among women who had a weight gain of 5.0 to 7.9 kg was 1.9 (95% CI, 1.5 to 2.3). The corresponding relative risk for women who gained 8.0 to 10.9 kg was 2.7 (CI, 2.1 to 3.3). In contrast, women who lost more than 5.0 kg reduced their risk for diabetes mellitus by 50% or more. These results were independent of family history of diabetes.

■ *Conclusion:* The excess risk for diabetes with even modest and typical adult weight gain is substantial. These findings support the importance of maintaining a constant body weight throughout adult life and suggest that the 1990 U.S. Department of Agriculture guidelines that allow a substantial weight gain after 35 years of age are misleading.

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The 1990 guidelines for adult weight published by the U.S. Department of Agriculture (1) recommend higher weights than previous standards. In particular, the guidelines for increased weight (about 7 kg on average) for persons age 35 years and older, with allowance for major weight gain in midlife, have stimulated much debate (2–4). The basis for these recommendations is unclear. The report by Andres (5) on which the recommendations may be based is fundamentally flawed because it ignored cigarette smoking. Although no apparent biological rationale exists for suggesting that persons increase their weight as they grow older, the health consequences of weight gain during adult life have not been clearly documented. In general, a strong association between body mass index and the risk for non–insulin-dependent diabetes mellitus has been observed. However, few studies have examined the consequences of weight gain during various periods of life. From a public health perspective, weight and weight gain are more easily understood than body mass index. Also, using change in weight as a basis for recommendations is attractive because it allows for differences in frame size, which are difficult to characterize. For these reasons, we quantified the relations between change in adult weight and the risk for non–insulin-dependent diabetes mellitus among women during 14 years of follow-up. We previously reported the relation between body mass index and clinical diabetes in this cohort after 8 years of follow-up (6).

Methods

Established in 1976, the Nurses' Health Study cohort consists of 121 700 female registered nurses aged 30 to 55 years who responded to a mail questionnaire about their medical history and health behaviors. Additional details have been reported elsewhere (7). The participants for our study were the 114 824 women who did not have diagnosed diabetes mellitus, coronary heart disease, stroke, or cancer when the cohort was enrolled in 1976. On the basis of a subsample of participants, we estimate that 98% of the participants are white, a percentage that reflects the ethnic background of women trained as registered nurses before 1977 (8).

Ascertainment of Risk Factors

Height and weight were ascertained on the 1976 questionnaire. On biennial follow-up questionnaires, we inquired about current weight and asked for information on whether diabetes mellitus, coronary heart disease, cancer, or other major illnesses had been diagnosed during the 2 years since the previous questionnaire. In 1980, we asked women to record their weight at age 18 years, and in 1982 we inquired about a history of diabetes in the

participants' mothers, fathers, brothers, or sisters. Weight reported by the participants in this study has been shown to be highly valid in two samples of Boston-area study participants. Self-reported current weight was highly correlated with measured weight (Spearman correlation coefficient, 0.97); the average measured weight was 1.5 kg lower (9, 10). In a substudy done in a cohort of nurses aged 27 to 44 years, recalled weight at age 18 years was compared with self-reported weights at ages 17 to 21 years that were recorded on nursing-school physical examination forms. The mean recalled self-reported body mass index was 21.6 kg/m^2 compared with an index of 22.1 kg/m^2 noted on the examination records (mean difference in weight, 1.4 kg). The Pearson correlation coefficient for weight was 0.87 and was independent of current age. Participants in the Nurses' Health Study cohort weighed, on average, 3 kg less than a national sample of women in 1976 (11). We used body mass index (weight in kg divided by height in m^2) as an index of relative weight and grouped it into 10 categories using whole-number cutpoints. We divided weight change between age 18 years and 1976 into eight categories. A body mass index of 24.0 kg/m^2 represents the 50th percentile for middle-aged, white U.S. women, and an index of 29.0 kg/m^2 represents the 75th percentile (11).

Diagnosis of Diabetes Mellitus

We mailed supplementary questionnaires on symptoms, diagnostic tests, and therapy for hypoglycemia to women who responded positively on any follow-up questionnaire to the query "Have you had physician-diagnosed diabetes mellitus?" The supplementary questionnaires were mailed in 1984 to women who reported that diabetes had been diagnosed between 1976 and 1984 and in 1986, 1988, and 1990 to women who reported diabetes on the questionnaires in those years. We excluded women who reported that diabetes had been diagnosed before they entered the study in 1976. An incident case of diabetes was confirmed if at least one of the following was reported on the supplementary questionnaire: 1) one or more classic symptoms (thirst, polyuria, weight loss, hunger, pruritus) plus a fasting plasma glucose level of at least 140 mg/dL (7.8 mmol/L) or a random plasma glucose level of at least 200 mg/dL (11.1 mmol/L); 2) two or more elevated plasma glucose values on different occasions (fasting level $\geq$140 mg/dL or random level $\geq$200 mg/dL, or both, or fasting level $\geq$200 mg/dL after 2 or more hours of testing for oral glucose tolerance) in the absence of symptoms; or 3) treatment with medication for hypoglycemia (insulin or oral hypoglycemic agent).

All women were 30 years of age or older at diagnosis. We excluded cases (and subsequent follow-up after diagnosis) of incident insulin-dependent (type 1) diabetes (n = 89). We also excluded women classified as having gestational diabetes only (diabetes first diagnosed during pregnancy and that persisted no more than 1 month after the end of pregnancy, with no subsequent diagnosis of diabetes when the woman was not pregnant). The remaining women with confirmed diabetes (n = 2204) were classified as having non–insulin-dependent diabetes mellitus; these women form the basis for our analysis. Our criteria for diabetes classification are consistent with those proposed by the National Diabetes Data Group (12)' except that we did not use any weight criteria in classifying diabetes.

To document the validity of the confirmation of diabetes by the supplementary questionnaire, we examined medical records in a random sample of the participants who reported diabetes. Of 84 women who reported diabetes and were classified as having non–insulin-dependent diabetes mellitus by supplementary questionnaires, 71 gave permission for review of their medical records; medical records were obtained for 62. An endocrinologist (JEM) who was unaware of the information reported on the supplementary questionnaires reviewed the available records using the National Diabetes Data Group criteria. The diagnosis of non–insulin-dependent diabetes mellitus was confirmed by medical records in 61 of the 62 women (98.4%).

Statistical Analysis

We computed incidence rates of non–insulin-dependent diabetes mellitus during the 14 years of follow-up for categories of body mass index calculated at baseline in 1976 and for categories of weight change between age 18 years and 1976. Follow-up began when the 1976 questionnaire was returned and ended on the date of death or diagnosis of diabetes, cardiovascular disease, or cancer, or 1 June 1990, whichever came first. Women who reported diabetes mellitus, coronary heart disease, stroke, or cancer on the baseline or follow-up questionnaires were excluded from subsequent follow-up. We obtained rates by dividing the number of incident cases by the number of person-years of follow-up in each category of body mass index or weight change. We computed relative risks as the rate of non–insulin-dependent diabetes mellitus in a specific category of body mass index divided by the rate among women with a body mass index less than 22.0 kg/m^2. Because family history was recorded in 1982, we repeated analyses from 1982 to 1990 to examine weight change within strata of family history and defined weight change in adulthood as weight in 1982 minus weight at age 18 years. We used proportional hazard models to simultaneously evaluate the association with family history, body mass index at age 18 years, and weight gain. We calculated 95% CIs for each relative risk.

Results

The mean weight $\pm$ SD of women in this cohort at age 18 years was 126.2 $\pm$ 19.4 pounds (57 $\pm$ 8.8 kg). Mean weight gain between age 18 years and 1976 varied monotonically with age from 7.6 pounds (3.4 kg) among women 30 years of age to 19.0 pounds (8.6 kg) for women 55 years of age. Reflecting these weight changes, the mean weight for each birth cohort (in single years) increased from 133 pounds (60.3 kg) for women 35 years of age to 144 pounds (65.3 kg) for women 55 years of age.

The risk for diabetes increased as attained body mass index increased over the 1976 value (index was updated every 2 years) (Table 1). Even women with a body mass index of 22.0 to 22.9 kg/m^2 had a significant threefold elevation in age-adjusted relative risk compared with women with an index less than 22.0 kg/m^2. Women of average weight (body mass index, 24 to 24.9 kg/m^2) had a relative risk of 5.0 (95% CI, 3.6 to 6.6) compared with women with an index less than 22 kg/m^2. Women with a body mass index of 31.0 kg/m^2 or more had an age-adjusted relative risk of 40.0 or greater (Table 1). This association persisted within age strata, and body mass index remained a strong risk factor, even for women as old as 69 years. After adjustment for body mass index, women aged 60 to 64 years had a relative risk of 3.4 (CI, 2.5 to 4.6) compared with women aged 40 to 44 years. The relation between body mass index and diabetes mellitus was similar in white and black women. The strong association between body mass index and the risk for diabetes mellitus persisted (that is, remained unchanged) when we repeated analyses that were limited to symptomatic cases of non–insulin-dependent diabetes mellitus (report of at least one symptom at diagnosis, including thirst, polyuria, weight loss, hunger, or pruritus).

To examine the association with early adiposity, we calculated the body mass index at age 18 years (Table 2). Women whose body mass index at age 18 years was greater than 22.0 kg/m^2 had a substantially elevated risk for clinical diabetes mellitus compared with women whose body mass index was less than 22.0 kg/m^2. For women whose body mass index was 33.0 to 34.9 kg/m^2 at age 18 years, the age-adjusted relative risk for diabetes was 6.6 (CI, 4.7 to 9.4). We repeated analyses using finer categories of body mass index at age 18 years and compared lean women with those whose body mass index was 21.0

Table 1. Attained Body Mass Index and Relative Risk for Non–Insulin-Dependent Diabetes Mellitus in U.S. Women Aged 30 to 55 Years in 1976 and Followed for 14 Years

Body Mass Index	Cases	Person-Years of Follow-up	Age-Standardized Incidence Rate*	Age-Adjusted Relative Risk (95% CI)
kg/m^2	*n*		%	
>22.0	55	466 052	13.0	1.0 (reference)
22.0–22.9	71	194 433	37.4	2.9 (2.0 to 4.1)
23.0–23.9	88	156 770	54.9	4.3 (3.1 to 5.8)
24.0–24.9	94	142 392	62.9	5.0 (3.6 to 6.6)
25.0–26.9	227	198 484	103.5	8.1 (6.2 to 10.5)
27.0–28.9	267	119 662	200.4	15.8 (12.7 to 19.8)
29.0–30.9	329	84 880	354.5	27.6 (22.7 to 33.5)
31.0–32.9	263	47 119	521.2	40.3 (33.7 to 48.3)
33.0–34.9	224	29 885	703.6	54.0 (45.6 to 64.0)
≥35.0	579	46 636	1190.5	93.2 (81.4 to 106.6)

* Rate per 100 000 persons standardized to the age distribution of length of follow-up in the cohort.

to 21.9 kg/m^2. The age adjusted relative risk was 0.8 for women with body mass indices of 20.0 to 20.9 kg/m^2, 19.0 to 19.9 kg/m^2, and 18.0 to 18.9 kg/m^2 (CIs, 0.7 to 1.0, 0.6 to 1.0, and 0.6 to 1.0, respectively).

We next categorized the weight change between age 18 years and the beginning of follow-up in 1976 to examine subsequent risk for diabetes. In an analysis adjusted only for age, in which women who gained weight were compared with those with stable weight, weight gain was strongly associated with risk for diabetes (Table 3). However, a modest positive association was also seen among women who lost 20 kg or more. Because weight loss of this magnitude occurred primarily among those who were initially overweight, the modest excess risk among those who lost weight would be confounded by earlier weight. Thus, after adjustment for body mass index at age 18 years, weight loss was associated with a greatly reduced risk for diabetes. In women who lost 20 or more kg between age 18 years and 1976, the risk for diabetes was greatly reduced (relative risk adjusted for age in 1976 and body mass index at age 18 years, 0.13 [CI, 0.05 to 0.29]) compared with women who lost less than 5 kg. After we controlled for body mass index at age 18 years, even women who lost 5.0 to 10.9 kg between age 18 years and 1976 had a substantial reduction in their risk for diabetes mellitus (relative risk, 0.54 [CI, 0.39 to 0.76]).

Compared with women who gained less than 5 kg (with adjustment for age and body mass index at age 18 years), women who gained 5.0 to 7.9 kg between age 18 years and 1976 had a relative risk of 1.9 (CI, 1.5 to 2.3), and women who gained 8.0 to 10.9 kg had a relative risk of 2.7 (CI, 2.1 to 3.3). The relative risk for women who gained 20.0 or more kg was 12.3 (CI, 10.9 to 13.8).

To examine whether the risks associated with weight change differed across strata of body mass index at age 18 years, we separately compared the age-adjusted relative risks for each level of weight gain with the risk for diabetes among women who had gained or lost fewer than 5 kg as of 1976 for each stratum of body mass index at age 18 years. The relative risk associated with weight gain decreased with higher body mass indices at age 18 years. However, at each level of body mass index at age 18 years, even modest weight gain was associated with an increased age-adjusted relative risk for diabetes mellitus (Table 4). A weight gain of 5.0 to 6.9 kg after age 18 years was associated with age-adjusted relative risks for diabetes that ranged from 1.6 (for women whose body mass index was at least 29.0 kg/m^2 at age 18 years) to 2.1 (for women whose body mass index was less than 22.0 kg/m^2) compared with women with the same body mass index at age 18 years who maintained a stable weight. For example, for women with a body mass index of at least

Table 2. Body Mass Index at Age 18 Years and Age-Adjusted Relative Risk for Diabetes in U.S. Women Aged 30 to 55 Years in 1976 and Followed for 14 Years

Body Mass Index at Age 18 Years	Cases*	Person-Years of Follow-up	Age-Standardized Incidence Rate†	Age-Adjusted Relative Risk (95% CI)	Relative Risk Adjusted for Age and Subsequent Weight Change (95% CI)
kg/m^2	*n*		%		
<22.0	830	797 107	104.3	1.0	1.0 (reference)
22.0–22.9	221	149 626	146.0	1.4 (1.2 to 1.6)	1.5 (1.3 to 1.8)
23.0–23.9	156	79 809	192.3	1.8 (1.5 to 2.2)	2.0 (1.7 to 2.4)
24.0–24.9	142	59 204	235.9	2.2 (2.0 to 2.7)	2.4 (2.0 to 2.9)
25.0–26.9	204	63 219	319.3	3.1 (2.6 to 3.5)	3.3 (2.8 to 3.9)
27.0–28.9	110	26 029	426.1	4.1 (3.5 to 5.0)	4.5 (3.7 to 5.5)
29.0–30.9	72	15 660	489.4	4.5 (3.6 to 5.6)	5.1 (4.0 to 6.5)
31.0–32.9	55	7475	709.8	7.0 (5.5 to 8.8)	9.6 (7.2 to 12.7)
33.0–34.9	24	3422	702.9	6.6 (4.7 to 9.4)	8.7 (5.7 to 13.2)
≥35.0	22	3152	700.4	6.6 (4.6 to 9.6)	13.5 (8.7 to 21.1)

* Data missing on weight at age 18 years for 368 cases during 286 625 person-years.
†Rate per 100 000 standardized to the age distribution of length of follow-up in the cohort.

Table 3. Age-Adjusted Relative Risk for Diabetes Mellitus during 14 Years of Follow-up and Weight Change between Age 18 Years and 1976

Weight Change (Amount)	Cases, *n**	Person-Years of Follow-up	Age-Adjusted Relative Risk	Relative Risk Adjusted for Age and Body Mass Index at Age 18 Years (95% CI)
Loss (≥20.0 kg)	5	5921	1.9	0.13 (0.1 to 0.3)
Loss (11.0 to 19.9 kg)	17	22 493	1.8	0.23 (0.1 to 0.4)
Loss (5.0 to 10.9 kg)	43	73 645	1.4	0.54 (0.4 to 0.8)
Loss (4.9 to a gain of 4.9 kg)	197	464 001	1.0	1.0 (reference)
Gain (5.0 to 7.9 kg)	130	192 123	1.5	1.9 (1.5 to 2.3)
Gain (8.0 to 10.9 kg)	143	132 630	2.2	2.7 (2.1 to 3.3)
Gain (11.0 to 19.9 kg)	545	211 126	5.2	5.5 (4.7 to 6.3)
Gain (≥20.0 kg)	724	93 840	15.1	12.3 (10.9 to 13.8)

* Data missing on weight change from age 18 years to 1976 for 400 cases during 295 552 person-years of follow-up.

29.0 kg/m^2, the relative risk associated with a weight gain of 5.0 to 6.9 kg was 1.6 (52.6/33.3 = 1.6). For women whose body mass index was 22.0 to 24.9 kg/m^2 at age 18 years and who had gained 5.0 to 6.9 kg since then, the relative risk for diabetes mellitus was 1.7 (4.8/2.9 = 1.7). These women, whose indices are still within guidelines for adult body mass index, have a significantly increased risk for diabetes. These relative risks were stable across strata of the participants' ages in 1976.

To address weight change during middle life and subsequent risk for diabetes mellitus, we calculated weight change during the 10 years between 1976 and 1986 and examined the risk for diabetes between 1986 and 1990. During these 4 years, we observed 762 cases of diabetes. Body mass index in 1976 was again the dominant risk factor for diabetes that was diagnosed between 1986 and 1990. Women whose body mass index in 1976 was 24.0 to 24.9 kg/m^2 had a relative risk of 5.0 (CI, 3.3 to 4.5) compared with women whose body mass index in 1976 was less than 22.0 kg/m^2. Relative risks increased to 49.0 (CI, 34.0 to 71.0) for women whose body mass index was greater than 35 kg/m^2. Compared with women who gained or lost less than 3.0 kg in those 10 years, women who gained 3.0 to 4.9 kg had an increased risk for diabetes mellitus (relative risk adjusted for age and body mass index in 1976, 1.5 [CI, 1.1 to 2.0]). Additional weight gain in middle age was associated with a greater increase in the relative risk for diabetes mellitus. Women who gained 10.0 kg or more had a relative risk of 1.8 (CI, 1.4 to 2.3). Women who lost 5.0 kg or more during the 10 years had an age-adjusted relative risk of 0.6 (CI, 0.4 to 1.0) compared with those who maintained a steady weight; women who lost 3.0 to 4.9 kg had an age-adjusted relative risk of 1.0 (CI, 0.6 to 1.5). These results were stable across strata of the participants' ages in 1976.

In this cohort, family history of diabetes was a predictor of risk for clinical diabetes. During 8 years of follow-up (from 1982 to 1990), we observed 1531 incident cases (799 346 person-years of follow-up). Women with one parent in whom diabetes was diagnosed (369 cases) had a relative risk adjusted for age and body mass index of 1.92 (CI, 1.70 to 2.17) compared with women without a family history of diabetes (1041 cases). Women with both a sibling and a parent having a history of diabetes (72 cases) had an age-adjusted relative risk of 2.78 (CI, 2.18 to 3.55). To examine the consistency of the weight-gain findings in strata of family history, we repeated the analysis using the time period 1982 to 1990. We observed that the association between weight gain from age 18 years to 1982 and the risk for diabetes mellitus adjusted for weight at age 18 years and current age was not altered by family history (Table 5).

Discussion

In these prospectively collected data, we observed a strong positive relation between body mass index and the risk for diabetes mellitus. Risk increased monotonically with body mass indices greater than 22.0 kg/m^2. Weight gain since age 18 years was strongly related to risk, and weight gain during middle age was also related, although the relative risks were smaller. In contrast, women who lost more than 5.0 kg between early adult life and the start of follow-up in 1976 had a substantially reduced risk for diabetes mellitus. These data were obtained from a cohort of predominantly white women. However, the

Table 4. Age-Adjusted Relative Risk for Diabetes Mellitus within Strata of Body Mass Index at Age 18 Years and Weight Change between Age 18 Years and 1976*

Body Mass Index at Age 18 Years, kg/m^2	Relative Risk (95% CI)					
	Loss of 5.0–10.0 kg	Loss or Gain of 4.9 kg	Gain of 5.0–6.9 kg	Gain of 7.0–10.9 kg	Gain of 11.0–19.9 kg	Gain of 20.0 or more kg
<22.0	1.0 (0.3 to 3.2)	1.0 (reference)	2.1 (1.4 to 3.2)	2.5 (1.8 to 3.6)	7.9 (6.0 to 10.5)	30.4 (23.1 to 40.1)
22.0–24.9	1.4 (0.7 to 2.8)	2.9 (2.0 to 4.1)	4.8 (2.9 to 8.0)	9.0 (6.2 to 13.0)	15.7 (11.6 to 2.12)	45.8 (34.3 to 61.2)
25.0–28.9	2.4 (1.2 to 5.1)	9.7 (6.6 to 14.3)	15.4 (8.4 to 28.1)	16.0 (9.9 to 26.0)	43.1 (31.3 to 59.4)	68.4 (50.0 to 94.0)
≥29.0	27.8 (17.1 to 45.1)	33.3 (21.8 to 51.0)	52.6 (25.9 to 106)	49.4 (29.0 to 84.2)	54.4 (35.0 to 84.8)	76.1 (50.6 to 115)

* Fourteen-year follow-up was from 1976 to 1990.

Table 5. Relative Risk for Diabetes Mellitus within Strata of Family History of Diabetes and Weight Change between Age 18 Years and 1982*

Family History	Relative Risk (95% CI)					
	Loss of 11 to 19 kg	Loss of 5 to 10 kg	Loss or Gain of 4.9 kg	Gain of 5 to 9 kg	Gain of 10 to 19 kg	Gain of 20 or more kg
No family history of diabetes	0.47 (0.18 to 1.3)	0.9 (0.6 to 1.7)	1.0	2.3 (1.7 to 3.1)	6.1 (4.7 to 7.9)	20.1 (15.6 to 25.9)
One parent with diabetes	2.1 (0.8 to 5.8)	1.9 (0.9 to 4.1)	3.6 (2.5 to 5.2)	6.8 (4.8 to 9.6)	12.6 (9.4 to 17.1)	27.9 (20.7 to 37.5)
Sibling alone with diabetes	–	4.3 (1.0 to 1.7)	1.0 (0.3 to 3.9)	5.8 (2.8 to 12.1)	11.9 (6.9 to 20.4)	32.8 (19.9 to 53.4)
Both parent and sibling with diabetes	–	3.7 (0.9 to 1.5)	1.6 (0.4 to 6.4)	11.7 (6.3 to 21.6)	21.3 (13.3 to 34.2)	48.7 (30.4 to 78.1)

* Relative risk adjusted for age and body mass index at age 18 years.

physiologic effects of weight gain are expected to be similar among other ethnic and racial groups. The limited numbers of cases precluded detailed analysis of weight change and the risk for diabetes in nonwhite women.

The prospective study design greatly reduces the probability of biased reporting of weight and avoids the problem of weight change after the diagnosis of diabetes mellitus, which can distort case-control studies. All women included in these analyses were free from diagnosed diabetes mellitus, cancer, and heart disease each time they recorded their weight. Incomplete follow-up is unlikely to distort these results because the overall follow-up rate was more than 90% and because rates were similar for each level of baseline body mass index. Because obese women are more likely to have screening tests for diabetes, the number of reported diagnoses among the heaviest women could be increased because of closer surveillance. This increase in reported diagnoses thus artificially increases the relation between body mass index and the risk for diabetes mellitus. However, in this population, neither the prevalence of reported symptoms at diagnosis nor the frequency of physician visits varied by level of body mass index. We also observed that the risk for diabetes mellitus was greatly elevated even at a body mass index of 25.0 k/m^2, a level that is well below standard clinical criteria for obesity and thus is unlikely to lead to any detection bias. Therefore, even women with a weight that is considered "normal" or average had an increased risk. Furthermore, the results did not change when we limited analyses to cases of diabetes in which symptoms were present at the time of diagnosis.

Body mass index is strongly correlated with the body fat mass (adjusted for height) as measured by densitometry, with a correlation coefficient of approximately 0.9 (13). To the extent that body mass index is an imperfect measure of adiposity, even the strong association between body mass index and diabetes mellitus that we observed may represent an underestimate of the true relation between adiposity and diabetes. Although the association between body mass index and the risk for diabetes has been examined across many studies, the strength of association has varied and has been most consistent for obese persons (6).

Few studies have addressed the relation between weight gain and the risk for diabetes mellitus, although many have reported relations between adolescent or adult obesity and the risk for subsequent diabetes (14). However, studies of short-term weight change among Pima Indians followed for 3.5 years showed that weight gain was associated with an increase in insulin resistance (15). In addition, findings from patients from an obesity clinic who were followed for 5 years show that weight gain is associated with deterioration in glucose tolerance, whereas weight loss improved glucose tolerance (16). Despite such studies, the magnitude of the association between weight change and subsequent diagnosis of diabetes mellitus has not often been quantified. In a previous analysis, we examined weight change but controlled for attained body mass index (6). Thus, we did not address the change in fat mass, which is modeled by controlling weight change for the body mass index before the weight change. Rather, controlling for attained body mass index models the duration of obesity because persons who are obese and have not changed weight have been obese longer than similarly obese participants who report recent weight gain (and therefore were leaner before the weight gain). In a detailed analysis of 142 cases of non–insulin-dependent diabetes mellitus among men and 142 cases among women in the Rancho Bernardo population, Holbrook and colleagues (17) reported that a weight gain of 10 pounds or more between 40 and 60 years of age was associated with a significant increase in the risk for diabetes mellitus (for men, the relative risk was 1.4 [$P < 0.05$]; for women, the relative risk was 1.7 [$P < 0.02$]). Adult weight gain (after age 18 years) was also associated with an increased risk after the investigators controlled for weight at age 18 years. The relative risk for diabetes mellitus was 1.4 for every 17% to 31% increase in weight since age 18 years (17).

In support of the Dietary Guidelines for Americans and the allowance for an increase in body mass index after age 35 years, Bray and Atkinson (3) have noted that "a small degree of weight gain in women during adult life is to be expected" and that "it carries little or no extra risk for adverse health events." Our results show clearly that even modest weight gain in adult life is associated with a twofold increase in the risk for diabetes mellitus.

These data strongly suggest that women can minimize the risk for diabetes by achieving a lean body build as a young adult and avoiding even modest weight gain throughout life. Furthermore, analyses limited to weight change in middle life (from 1976 to 1986) indicated that weight gain at any age (up to 65 years) is associated with an increased risk for diabetes mellitus among women. Major weight increases in adult life are likely to increase rather than decrease the risk for morbidity and mortality

(18, 19). Obesity is a major, increasing problem in the United States (20). These data should help guide physicians to counsel patients on maintaining weight and avoiding any further weight gain.

In summary, weight gain of even 7.0 to 10.9 kg after age 18 years was associated with a twofold increase in the risk for diabetes, and an adult body mass index of 23.0 to 25.0 kg/m^2 (a weight of 134 to 146 pounds for a women 5 feet 4 inches tall) was associated with a fourfold increased risk for diabetes mellitus compared with women whose body mass index was less than 22.0 kg/m^2. Middle-aged women who lose more than 5.0 kg have a significantly reduced risk for diabetes mellitus compared with women with stable weight. Thus, these findings suggest that the 1990 U.S. Department of Agriculture guidelines, which imply that substantial weight gains at age 35 years and a body mass index as high as 27.0 kg/m^2 are healthy, may be misleading.

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