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WEIGHT AS A RISK FACTOR FOR CLINICAL DIABETES IN WOMEN

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To determine the relation of body mass index (weight/height^2) with the risk of clinical non-insulin-dependent diabetes, the authors analyzed data from a cohort of 113,861 US women aged 30–55 years in 1976. During 8 years of follow-up (826,010 person-years), 873 definite cases were identified among women initially free from diagnosed diabetes. Among women of average body mass index, 23–23.9 kg/m^2, the relative risk was 3.6 times that of women having a body mass index less than 22 kg/m^2. The risk continued to increase above this level of body mass index. The authors observed a much weaker positive association with weight at age 18, and this association was eliminated after adjustment for current body mass index. Thus, weight gain after age 18 was a major determinant of risk. For an increase of 20–35 kg, the relative risk was 11.3, and for an increase of more than 35 kg, the relative risk was 17.3. Adjusting for family history did not appreciably alter the strong relation observed among women at average levels of body mass index. These data indicate that, at even average weight, women are at increased risk of clinical non-insulin-dependent diabetes and that the relation between body mass index and risk of diabetes is continuous.

diabetes mellitus, non-insulin-dependent; incidence; obesity; women

The reported incidence of non-insulin-dependent diabetes has been increasing steadily (1). Diabetes is currently the seventh leading cause of death in the United States (2) and is a major risk factor for premature coronary heart disease and stroke (3). Non-insulin-dependent diabetes has been conservatively estimated to have an annual economic impact of 11.6 billion dollars (4). The degree of obesity and subsequent incidence of diabetes have been investigated in several prospective studies, although most of these have been small (5–14) and have included few women. The largest study among women followed 32,662 obese white women and, hence, provided

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Abbreviation: CI, confidence interval.

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little information on average body mass index (15). In general, a positive association has been observed between body mass index and the risk of diabetes (16).

Obesity is characterized by a reduced number of insulin receptors and insulin resistance (17, 18), which is reversible with weight loss (19, 20). Thus, the combination of epidemiologic and metabolic data leaves little doubt that obesity is causally related to non-insulin-dependent diabetes (21). Nonetheless, the quantitative relation between body mass index and the risk of diabetes is less well defined, particularly among women. Moreover, the contribution of obesity at differing periods in life and the effect of weight gain in adulthood to subsequent risk of diabetes have not been clearly quantified. In particular, the risks associated with moderate levels of overweight have not been adequately addressed. We therefore examined the magnitude of the risk of diabetes across the full range of body mass index, both current and past, in a large cohort of US women.

MATERIALS AND METHODS

The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses, aged 30–55 years, living in 11 US states returned a mailed questionnaire (22, 23). On the basis of a subsample of 249 participants, we estimate that 98 percent are white.

Height and weight were ascertained on the 1976 questionnaire. On biennial follow-up questionnaires mailed to all cohort members, we inquire about current weight and also seek information on the diagnosis of diabetes, coronary heart disease, cancer, and other major illnesses during the 2-year period since the previous questionnaire. In 1980, we asked the women to record their weight at age 18, and in 1982, we inquired about a history of diabetes in the mother, father, brothers, or sisters of participants. Weight reported by the participants in this study has been shown to be valid among 184 Boston area study participants, and self-reported current weight was highly correlated with measured weight (Spearman's correlation coefficient, $r = 0.95$), although it averaged 1.5 kg lower (24). Participants in the Nurses' Health Study cohort weigh, on average, 3 kg less than a national sample of women. A body mass index of 24 kg/m^2 represents the 50th percentile, and 29 kg/m^2 represents the 75th percentile for middle-aged white US women (25). We used 10 categories of body mass index, choosing whole number cut points to facilitate comparisons with previous studies.

Population for analysis

Among the 121,700 women enrolled in the Nurses' Health Study, 117,020 of these were free from diagnosed diabetes, coronary heart disease, and cancer in 1976. Of these, 113,861 women provided height and weight information in 1976 and responded to at least one follow-up questionnaire, thus forming the population for analyses.

Non-insulin-dependent diabetes

In 1984, we mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and treatment to the 2,120 women who had responded positively on any of the follow-up questionnaires to the question, "Have you had diabetes mellitus diagnosed?" A total of 140 women did not respond to the mailings of the supplementary questionnaire, 110 women denied the diagnosis of diabetes, and 192 women reported a date of diagnosis on the supplementary questionnaire that was earlier than the return of their 1976 questionnaire and, thus, were excluded. In addition, 113 women reported the diagnosis of cancer, and 83 women reported the diagnosis of coronary heart disease before the diagnosis of diabetes. These cases were also excluded from analysis because weight may change as a consequence of the diagnosis of these diseases, and patients under care may be under greater surveillance. On the basis of the responses, we excluded 25 incident cases of insulin-dependent (type 1) diabe-

tes, defined as 1) classic symptoms with fasting plasma glucose ≥140 mg/dl, random plasma glucose ≥200 mg/dl, or at least two elevated plasma glucose levels if no symptoms; 2) continuous insulin therapy commencing within 1 year of diagnosis; and 3) hospitalization for ketoacidosis. In addition, we excluded 11 women classified as having gestational diabetes. The remaining women were included in this analysis if they were classified as having definite non-insulin-dependent diabetes, which required reporting one of the following: 1) at least one classic symptom (weight loss, hunger, thirst, polyuria, pruritus) plus plasma fasting glucose ≥140 mg/dl or random plasma glucose ≥200 mg/dl; or 2) at least two elevated plasma glucose levels ≥200 mg/dl in the absence of symptoms. Because our principal focus in this analysis is the relation between body mass index and diabetes, no weight criterion was used in the classification of type of diabetes mellitus, but definitions are otherwise consistent with those proposed by the National Diabetes Data Group (26). In total, we confirmed 873 definite cases of non-insulin-dependent diabetes that were diagnosed after the date of return of the 1976 questionnaire and before June 1, 1984.

To document the validity of self-reported diabetes, we requested medical records from a random sample of 84 women reporting diabetes and classified as definite non-insulin-dependent diabetes by supplementary questionnaire. Seventy-one women gave permission for medical record review. An endocrinologist (J. E. M.) who was blinded to the information reported on the supplementary questionnaire reviewed the 62 records that we received, using the National Diabetes Data Group criteria (26). Sixty-one of 62 women classified as having definite non-insulin-dependent diabetes by questionnaire response were confirmed by medical record review.

Data analysis

The body mass index (kg/m^2) is used as a measure of adiposity. We allocate person-time to each woman according to her level of body mass index at the beginning of each follow-up interval. We calculate incidence rates by dividing the number of incident cases by the number of person-years of follow-up for each category of body mass index. Relative risks are computed as the incidence rate in a specific category of body mass index divided by the incidence rate in the lowest category, after adjustment for 5-year age intervals (27). The Mantel extension test (27) is used to evaluate the linear trend of increasing risk with increasing body mass index in data stratified by age. To determine whether the effect of earlier body mass index is modified by current body mass index, we examined the age-adjusted relative risks of weight at age 18 within categories of current body mass index. We also used proportional hazards models (27), controlling for age and follow-up interval, to examine the relations between body mass index or weight change and the risk of diabetes and to estimate 95 percent confidence intervals.

We calculate the attributable risk (rate difference) and the attributable risk (percentage)

$$\text{Attributable risk (\%)} = \frac{\text{difference between incidence rates}}{\text{absolute risk in each Quetelet category}} \times 100$$

for different levels of body mass index (28). The attributable risk is a measure of the absolute effect of obesity and provides a direct estimate of the public health impact of body mass index in terms of the number of cases of non-insulin-dependent diabetes that could theoretically be prevented by elimination of obesity.

RESULTS

The risk of diabetes increased steadily with higher weight; women weighing more than 70 kg experienced an approximately

24-fold risk compared with those weighing less than 55 kg. We observed no overall relation of height with risk of diabetes.

The association observed for diabetes with weight is substantially increased when weight is adjusted for height, using body mass index (see table 1 and figure 1). An extremely strong relation is seen within each 5-year age group (for each age stratum, the Mantel extension χ for trend was greater than +10, $p \ll 0.001$). The relative risk of diabetes is elevated for women with body mass index greater than 22 kg/m^2 and is particularly pronounced for those with body mass index greater than 25 kg/m^2. Among women with a body mass index of 22–22.9 kg/m^2, the proportional hazards relative risk of diabetes is 2.1 (95 percent confidence interval (CI) 1.4–3.3) compared with that in women with a body mass index less than 22 kg/m^2, and for women with a body mass index of 23–23.9 kg/m^2, the proportional hazards relative risk was 3.5 (95 percent CI 2.3–5.1). Women at a body mass index of 25–26.9 had more than a fivefold increase in risk of diabetes. These relative risks were stable across age strata and did not vary materially with follow-up interval.

The attributable risk of diabetes likewise rose with body mass indexes of 22 kg/m^2 or greater. For a body mass index of 25–26.9 kg/m^2, the attributable risk (the rate of diabetes among women with a body mass index of 25-26.9 kg/m^2 minus the rate among women with a body mass index less than 22 kg/m^2) is 72.1 cases per 100,000 person-years. This rises with increasing body mass index. For women with a body mass index of 33 kg/m^2 or more, 98 percent of diagnoses of diabetes are attributable to obesity. Within the total cohort, 90.4 percent of diagnoses of diabetes are attributable to a body mass index greater than 22 kg/m^2.

To examine the effect of early obesity, we calculated the body mass index at age 18 (table 2). Data on weight at age 18 were provided by 92,052 women. For women with

TABLE 1

Age, body mass index, and risk of diabetes among a cohort of US women aged 30–55 years in 1976 and followed for 8 years

Body mass index (kg/m^2)	Age group										Age-adjusted relative risk	Proportional hazards relative risk*
	30–39 years		40–44 years		45–49 years		50–54 years		55–64 years			
	Cases	Person-years	Cases	Person-years	Cases	Person-years	Cases	Person-years	Cases	Person-years		
<22	11	110,777	9	67,075	9	55,876	10	46,433	4	24,921	1.0	1.0
22–22.9	7	27,062	8	20,589	6	19,568	5	18,195	5	10,020	2.2	2.1 (1.4–3.3)†
23–23.9	8	22,262	3	18,481	11	18,740	18	18,776	9	10,961	3.6	3.5 (2.3–5.1)
24–24.9	6	17,758	4	15,518	7	16,499	13	17,211	7	10,491	3.1	2.9 (1.9–4.5)
25–26.9	9	20,486	8	18,529	25	21,441	19	23,184	25	14,420	5.5	5.2 (3.7–7.5)
27–28.9	10	11,970	13	11,443	25	13,142	24	14,047	24	9,038	10.1	9.6 (6.8–13.6)
29–30.9	9	8,437	21	8,290	28	9,520	46	9,947	31	6,294	20.0	19.0 (13.6–26.4)
31–32.9	13	4,815	14	4,712	19	5,223	38	5,565	27	3,431	29.6	28.0 (19.9–39.4)
33–34.9	6	3,022	8	2,752	21	2,920	26	3,075	25	1,892	40.2	38.5 (27.0–54.9)
≥35	22	4,762	37	4,430	63	4,896	49	4,525	28	2,587	60.9	58.2 (42.4–79.9)

* Proportional hazards model including follow-up interval, age, and body mass index.
† Numbers in parentheses, 95 percent confidence interval.

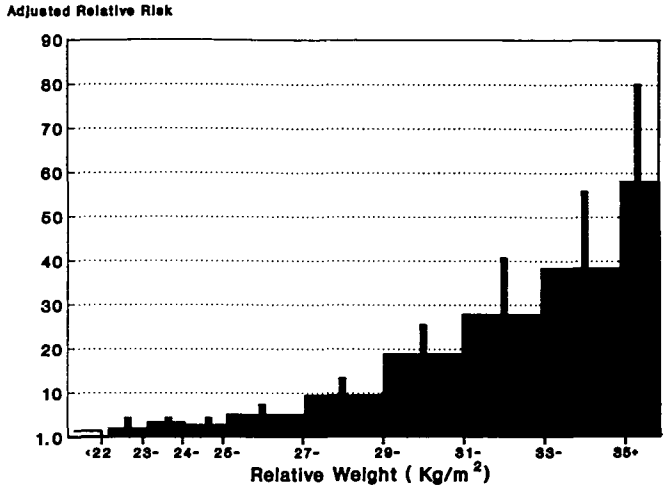

FIGURE 1. Relative risk of non-insulin-dependent diabetes mellitus according to levels of body mass index among women 30–55 years of age in 1976, adjusted for age.

TABLE 2

Body mass index at age 18 and age-adjusted risk of diabetes among a cohort of US women aged 30–55 years in 1976 and followed for 8 years

Body mass index at age 18 years (kg/m²)	Person-years	Cases*	Age-adjusted relative risk	Relative risk adjusted for current relative weight†
<19	129,038	99	1.0	1.0
19.0–19.9	112,847	61	0.7	0.7
20.0–20.9	130,548	90	0.9	0.7
21.0–21.9	109,274	99	1.2	0.8
22.0–22.9	67,799	81	1.6	0.8
23.0–23.9	47,835	66	1.8	0.7
24.0–24.9	35,028	57	2.1	0.6
25.0–26.9	33,257	84	3.3	0.8
27.0–28.9	15,273	48	4.2	0.8
≥29	17,329	80	6.1	0.8

* Data on body mass index at age 18 missing for 108 cases.

† Relative risk adjusted for age in 5-year intervals, follow-up interval, and body mass index at the beginning of each follow-up interval.

a body mass index greater than or equal to 29 kg/m² at age 18 years compared with those with a body mass index of less than 19 kg/m², the age-adjusted relative risk of diabetes is 6.1 (95 percent CI 4.7–7.9). Body mass index at age 18 is strongly correlated with current body mass index ($r = 0.52$). After controlling for current body mass index, age, and follow-up interval in a proportional hazards model, the positive association with body mass index at age 18 is completely eliminated (relative risk for 29 kg/m² = 0.8, 95 percent CI 0.6–1.1). In this model, the effect of current body mass index remains essentially unchanged, indicating the dominance of current body mass index over body mass index at age 18.

We also used these data to examine the association of weight change from age 18 to the beginning of each follow-up interval with the subsequent risk of diabetes (see figure 2). Only 11 cases of diabetes occurred

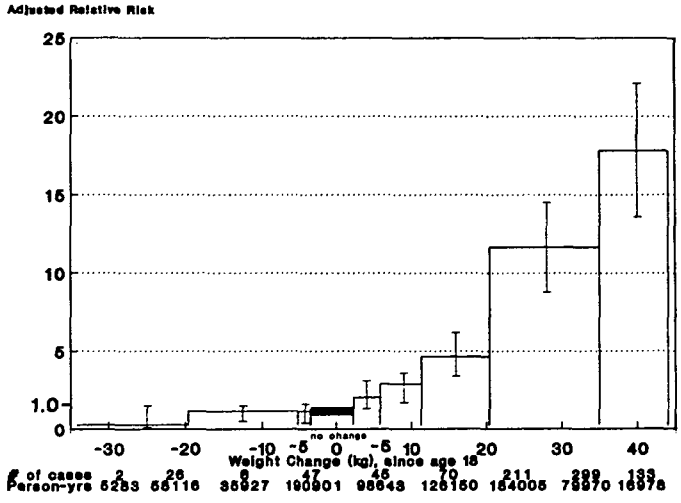

FIGURE 2. Relative risk of non-insulin-dependent diabetes mellitus according to weight change from age 18 in a cohort of US women, adjusted for age and body mass index at age 18.

among women who had a body mass index at age 18 less than 21 kg/m^2 (53 percent of the cohort providing data on weight at age 18 fell into this category) and who gained less than 3 kg. After controlling for body mass index at age 18, women who gained more than 3 kg were at substantially higher risk of diabetes compared with those who had less than a 3-kg weight change. Compared with women with stable weight, the relative risk for a 10- to 20-kg weight gain after adjusting for age and body mass index at age 18 is 4.6 (95 percent CI 3.4–6.2), for a 20- to 35-kg weight gain, the relative risk is 11.3 (95 percent CI 8.8–14.5), and for a >35-kg gain, the relative risk is 17.3 (95 percent CI 13.6–22.1).

To examine the effect of recent weight gain, we classified women according to change in weight from 1976 to 1980 and analyzed their risk of diabetes during the 1980–1984 interval. In a multivariate model controlling for body mass index in 1976 (in six categories that reflected increasing risk of diabetes) and age, women who gained 10–20 kg in 4 years experienced twice the risk of diabetes compared with women whose weight change was less than 1 kg (relative risk = 2.0, 95 percent CI 1.5–2.7) (table 3). Among the subgroup of women with a body mass index greater than 27 kg/m^2 in 1976, those who lost 5–20 kg between 1976 and 1980 had a trend toward a reduced risk of diabetes between 1980 and 1984 compared with women whose weight changed less than 1 kg (age-adjusted relative risk = 0.7, 95 percent CI 0.5–1.1).

The effect of family history was examined prospectively for cases arising after the return of the 1982 questionnaire (when the family history data were collected from 100,774 participants). During the 1982–1984 interval, 251 cases of diabetes occurred; 159 of these cases were among women with no previous family history of diabetes. Compared with that in women who reported no family history of diabetes in a first degree relative, the age-adjusted relative risk of diabetes for women with only one parent with diabetes was 2.5 (95 percent CI 1.9–3.2); for siblings alone or a sibling and a parent with diabetes, the relative risk was 2.4 (95 percent CI 1.5–3.8). After controlling for age and current body mass index in 1982, we found that these relative risks for family history were considerably reduced. Compared with risk in women with no family history of diabetes, for only one parent with diabetes the adjusted relative risk was 2.0 (95 percent CI 1.5–2.6), and for sibling alone or a sibling and a parent with diabetes the adjusted

TABLE 3

*Weight change between 1976 and 1980 and relative risk of diabetes from 1980 to 1984 according to the level of body mass index in 1976**

Weight change 1976–1980 (kg)	Body mass index																Relative risk, age and related weight adjusted
	<22			22–24.9			25–26.9			27–28.9			29–31.9		≥32		
	Cases	Women	Relative risk†	Cases	Women	Relative risk	Cases	Women	Relative risk	Cases	Women	Relative risk	Cases	Women	Relative risk	Cases	Women	Relative risk	
−20 to −5.0	1	309	3.8	0	604		6	1,115	1.6	3	555	0.3	11	576	0.7	24	594	0.9	0.84 (0.6–1.2)‡
−4.99 to −3.0	3	1,176	2.9	1	1,131	0.4	8	1,135	2.1	3	386	0.5	6	331	0.6	13	223	1.3	1.06 (0.7–1.6)
−2.99 to −1.0	0	3,222		2	2,160	0.5	5	1,708	0.8	6	475	0.8	7	405	0.6	11	219	1.0	1.00 reference
−0.99 to +0.99	7	7,712	1.0	7	3,535	1.0	10	2,744	1.0	13	786	1.0	20	703	1.0	25	515	1.0	0.86 (0.6–1.2)
1.00 to 2.99	6	9,676	0.7	3	4,376	0.4	12	3,173	1.0	12	791	0.9	12	624	0.7	18	328	1.2	0.86 (0.6–1.2)
3.00 to 4.99	6	5,871	1.2	4	3,336	0.6	19	2,927	1.8	9	829	0.7	12	704	0.6	28	456	1.3	1.06 (0.8–1.4)
5.00 to 9.99	6	3,094	2.1	8	2,493	1.7	22	2,666	2.6	17	921	1.3	23	820	1.1	31	550	1.2	1.50 (1.2–2.0)
10.00 to 19.99	1	539	2.0	1	599	0.9	19	965	4.4	10	434	1.8	20	404	2.0	21	384	1.2	2.00 (1.5–2.7)

* Among a cohort of 93,794 US women who provided data on weight in 1976 and 1980 and who responded to either the 1982 or 1984 follow-up questionnaires.
† Relative risk = age-adjusted relative risk.
‡ Numbers in parentheses, 95 percent confidence interval.

relative risk was 1.8 (95 percent CI 1.2–2.9). During the 1982–1984 follow-up interval, the age-adjusted relative risk of diabetes among women with a body mass index of 22.0–28.9 compared with a body mass index of less than 22 kg/m^2 was 6.2 (95 percent CI 3.1–12.2) without adjustment for family history of diabetes; additional adjustment for family history reduced this only slightly (relative risk = 5.9, 95 percent CI 3.0–11.7) (see table 4).

We next explored the potential for diagnostic bias to account for the relations observed between increasing body mass index and risk of diabetes. We considered the possibility that physicians, knowing the associations between obesity and diabetes, may be more likely to diagnose diabetes in fatter women. When we examined the self-reports of symptoms present at the time of diagnosis of diabetes, however, we observed that the classic symptoms were reported with about equal frequency at each level of body mass index. If there were a material difference in diagnosis, one would have predicted the obese women diagnosed with diabetes to have reported fewer symptoms than the leaner diabetics. In this cohort, the proportion of women diagnosed without classic symptoms (i.e., by screening) was similar across categories of body mass index; χ trend = 0.39, p = 0.7 (see table 5). In 1978, women reported whether or not they had visited a physician in the preceding year. Overall, we observed that 68 percent of women reported an office visit during the year. Because obese women may be more likely to visit a physician, and therefore more likely to be screened for non-insulin-dependent diabetes mellitus, we compared the frequency of office visits within each level of body mass index (see table 5). Among women who remained free from diabetes during the follow-up from 1978 to 1984, we observed little relation between level of obesity and physician visits. The proportion reporting a physician visit rose from 67 percent among women having a body mass index less than 22 kg/m^2 to 73 percent among women with a body mass index 35 kg/m^2 or more (χ trend =

TABLE 4

Body mass index, family history, and relative risk of diabetes from 1982 to 1984 in a cohort of 82,609 US women aged 36–41 years in 1982

Body mass index (kg/m^2)	No family history			One parent history			Sibling alone or sibling plus parent			Relative risk	
	Cases	Person-years	Relative risk	Cases	Person-years	Relative risk	Cases	Person-years	Relative risk	Age adjusted only	Adjusted for age and family history
<22	5	38,678	1.0	2	6,878	1.0	0	1,554		1.0	1.0
22.0–28.9	45	73,027	5.2 (2.3–11.7)*	23	14,030	5.6 (1.5–21.0)	9	3,468		6.2 (3.1–12.2)	5.9 (3.0–11.7)
≥29	109	18,181	48.8 (29.5–78.5)	47	4,531	36.0 (14.4–89.8)	11	1,274		50.1 (32.6–77.1)	47.1 (30.3–73.1)
Relative risk adjusted for age			1.0			2.5 (1.9–3.2)			2.4 (1.5–3.8)		
Relative risk adjusted for age and body mass index			1.0			2.0 (1.5–2.6)			1.8 (1.2–2.9)		

* Numbers in parentheses, 95 percent confidence interval.

6.27, $p < 0.01$). Although, among women who subsequently reported the diagnosis of diabetes, a greater proportion had reported a physician visit in 1978, this was also independent of body mass index. These data suggest that, in this cohort of nurses, there was no substantial diagnostic bias by level of body mass index. Further, this trend could not explain away the relative risks we observed.

DISCUSSION

In these prospectively collected data, we observed an extremely strong positive relation between level of body mass index and the risk of diabetes. Risk increased with levels of body mass index above 22 kg/m^2. Women at average weight were at increased risk compared with women with a body mass index less than 22 kg/m^2. Weight gain after age 18 was associated with an increased risk compared with women whose weight did not change after age 18. After adjusting for current weight, a higher body mass index at age 18 did not confer any increase in risk of diabetes, reflecting the dominance of current over former body mass index. Within this cohort overall, 90.4 percent of diabetes diagnoses (144 cases per 100,000 person-years) can be attributed to a body mass index greater than 22 kg/m^2.

The prospective design of this study greatly reduces the probability of biased reporting of weight and avoids the problem of weight change following the diagnosis of diabetes, which can be a serious problem in case-control studies. All women included in these analyses were free from diagnosed diabetes, cancer, and heart disease each time they recorded their weight. Incomplete follow-up is unlikely to distort these results, since the follow-up rate was over 90 percent and similar for each level of baseline body mass index. Obese women are almost surely more likely to have screening tests for diabetes. Hence, the number of reported diagnoses among the heaviest women would

TABLE 5

Number and percentage of cases by category of body mass index among a cohort of US women who reported each symptom at the time of diagnosis and who reported at least one physician visit in 1978

Body mass index (kg/m²)	Total cases*	% reporting no classical symptoms	Weight loss	Hunger	Thirst	Pruritus	Polyuria	Physician visits†	
								Diabetes	No diabetes
Total no. of subjects reporting symptoms			167	231	508	349	457	492	63,371
<22	43	15	20 (47)‡	17 (40)	31 (72)	18 (42)	28 (65)	21 (72)	23,169 (67)
22–22.9	31	30	10 (32)	11 (35)	18 (58)	12 (39)	18 (58)	11 (65)	7,245 (66)
23–23.9	49	36	10 (20)	11 (22)	26 (53)	15 (31)	26 (53)	29 (81)	6,862 (67)
24–24.9	37	39	8 (22)	13 (35)	16 (43)	7 (19)	17 (46)	16 (80)	5,921 (68)
25–26.9	86	27	20 (23)	23 (27)	48 (56)	34 (40)	46 (53)	47 (72)	7,423 (68)
27–28.9	96	28	16 (17)	27 (28)	52 (54)	34 (35)	46 (48)	62 (86)	4,721 (69)
29–30.9	135	35	24 (18)	25 (19)	75 (56)	53 (39)	57 (42)	79 (77)	3,313 (70)
31–32.9	111	28	19 (17)	25 (23)	67 (60)	39 (35)	59 (53)	65 (74)	1,940 (70)
33–34.9	86	22	18 (21)	24 (28)	57 (66)	38 (44)	49 (57)	42 (71)	1,049 (72)
≥35	199	24	22 (11)	55 (28)	118 (59)	99 (50)	111 (56)	120 (78)	1,728 (73)

* Total cases applies to categories of weight loss, hunger, thirst, pruritus, and polyuria only, based on the cases diagnosed after the return of the 1976 questionnaire.

† Proportion of those who subsequently developed diabetes and of those who remained free from diabetes that indicated they had visited a physician.

‡ Numbers in parentheses, percentage.

be increased because of closer surveillance, which artificially increases the relation between body mass index and risk of diabetes. In this population, however, the prevalence of reported symptoms at diagnosis did not vary by level of body mass index, nor did the frequency of physician visits. Moreover, the proportion of cases without a history of prior symptoms (29 percent) varied only a small amount across all levels of body mass index, indicating that any tendency toward increased detection of asymptomatic cases among the obese was modest and was unlikely to be biased among women of average body mass index. Further, we observed that the risk of diabetes rose sharply from a body mass index of 22 kg/m², a level well below standard clinical criteria for obesity and, thus, unlikely to lead to detection bias. Therefore, even women of average weight were at increased risk. The age-specific incidence rates for women in this study are comparable to those reported by Melton et al. (29) for white women in Minnesota. Furthermore, recent data reported from the Second National Health and Nutrition Examination Survey show that, among participants aged 40–70 years without a parental history of diabetes, the ratio of diagnosed to undiagnosed diabetes was 0.72 among nonobese subjects and 0.90 among obese subjects, indicating only a moderate tendency to preferentially overdiagnose diabetes among obese persons in the general population (30).

It is well known that many prevalent cases of diabetes are not diagnosed. Any general underdiagnosis, however, would have little impact on the relative risks so long as the proportion of undiagnosed cases did not vary substantially by level of body mass index. Given the greater ascertainment of cases among the most obese suggested by the Second National Health and Nutrition Examination Survey, the relative risks for women with a body mass index greater than 32 kg/m² are likely to be inflated. The results for women at average weight, however, are unlikely to be biased.

Classification of diabetes was based on a

supplementary questionnaire completed by the nurse participants in this study; several lines of evidence indicate that this diagnosis was highly specific. Medical records from a sample of women classified as having non-insulin-dependent diabetes according to self-reported data provided a high level of confirmation (98 percent). Furthermore, self-reported diabetes is a strong predictor of cardiovascular disease in this cohort (31), consistent with other epidemiologic studies. We avoided any use of body mass index as a criterion for defining the cases and, thus, may have included in the non-insulin-dependent category some women with insulin-dependent diabetes of maturity onset who had not been hospitalized for ketoacidosis but had documented ketonuria and were lean. Because these women are lean, this would have resulted in an underestimate of the effects of higher levels of body mass index. The number of such insulin-dependent cases arising in this middle-aged population, however, if any, is likely to be quite small (32).

Body mass index is moderately to highly correlated with the percentage of body fat measured by densitometry; correlation coefficients (based mostly on men) range between 0.5 and 0.8 (33–36). To the extent that body mass index is an imperfect measure of adiposity, even the very strong association between body mass index and diabetes that we observed may represent an underestimate of the true relation between adiposity and diabetes.

The association between body mass index and the risk of diabetes has been examined in only a few prospective studies which have focused primarily on risk associated with high levels of body mass index. Westlund and Nicolaysen (6) followed 2,399 men for 10 years and documented 44 incident cases of diabetes on the basis of a review of medical records for physician diagnoses; they observed a relative risk of 24 for men greater than 45 percent overweight compared with men of normal weight. Similar results were reported by Ohlson et al. (5), who defined diabetes as "physician diagnosis" or fasting venous blood glucose ≥7 mmol/liter or a glucose value ≥10.0 mmol/liter 2 hours after an oral glucose level of 100 g, and by Modan et al. (8), who administered an oral glucose tolerance test as part of the follow-up procedures for subjects with a history of physician diagnosis of diabetes who were not taking insulin. Subjects with a casual blood glucose >130 mg/100 ml were also classified as diabetic (8). Knowler et al. (10) followed 3,137 Pima Indians for up to 15 years. Each follow-up examination included an oral glucose tolerance test. They observed 340 cases of non-insulin-dependent diabetes and reported a nearly linear increase in risk of diabetes with increasing body mass index. During 1,322 person-years of follow-up for women aged 35–64 years, the age-adjusted relative risk of diabetes among the Pima Indians was 1.5 (95 percent CI 0.6–3.7) for those with a body mass index greater than 30 kg/m^2 compared with a body mass index less than 25 kg/m^2; in this age group, however, only two person-years were accrued by women with a body mass index less than 20 kg/m^2. Medalie et al. (7) followed 8,688 Israeli men over 5 years and observed a relative risk that was 2.5 for men with a body mass index of more than 27 kg/m^2 compared with a body mass index less than 24 kg/m^2. Likewise, in The Framingham Study (9) with criteria that include impaired glucose tolerance as well as true non-insulin-dependent diabetes mellitus and in the Tecumseh population where diabetes was classified according to physician diagnosis and therapy with insulin or hypoglycemic agents (11), a higher body mass index was significantly associated with risk of diabetes. Although a direct association has been consistently observed in previous studies, the strength of association has been most consistent for the very obese (37). The modest number of incident cases of diabetes in these previous investigations necessitated a crude categorization of body mass index and inclusion of people at the

average level of body mass index in the reference category. In contrast, the large number of cases in our study permitted a much finer grouping according to body mass index, thus providing the opportunity to examine the effects of minimal degrees of adiposity.

In addition to the overall degree of obesity, body fat distribution has important health effects (37–40). Ohlson et al. (5) have recently reported that abdominal obesity increases the risk of diabetes among men independently of body mass index, confirming previous cross-sectional data (41–43). This is consistent with laboratory data that show decreased insulin receptor activity with abdominal adiposity (44). Measurements to assess fat distribution are not available in the Nurses' Health Study for the time period encompassed in this report.

To avoid the likely bias introduced by retrospective ascertainment of family history of diabetes, we used our data only prospectively from 1982 to 1984. In this 2-year period, the majority of cases occurred in women without a family history of disease. Consistent with previous reports, a family history of diabetes was a significant risk factor (1, 45, 46); a positive family history for diabetes, however, was not nearly as strong a risk factor for non-insulin-dependent diabetes as was body mass index. The strength of association observed for family history may still be overestimated because of bias, with relatives of diabetics more likely to be screened for diabetes. In our analysis, average levels of body mass index remained a strong risk factor for diabetes even after controlling for family history.

These data indicate that the risk of non-insulin-dependent diabetes in US women is elevated even at average weight and rises progressively with increasing body mass index. The association between current body mass index and risk of diabetes has important public health implications, since obesity is extremely common (47, 48). The underlying etiologies of obesity are beyond the scope of this analysis, but probably represent a complex interaction between genetic factors and sedentary life-style in the environment of an unconstrained food supply (49). In these data, current body mass index and recent weight gain are clearly associated with an increasing risk of diabetes. Thus, the prevention of obesity should very likely reduce the incidence of non-insulin-dependent diabetes.

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