A Prospective Study of Obesity and Risk of Coronary Heart Disease Among Diabetic Women

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OBJECTIVE — To examine the relationship of obesity, measured as BMI, and weight change to incidence of coronary heart disease (CHD) among women with diabetes.

RESEARCH DESIGN AND METHODS — We followed 5,897 women with type 2 diabetes in the Nurses' Health Study for ≤20 years. Women were aged 40–74 years and had no history of cardiovascular disease or cancer at the beginning of the follow-up period. BMI values from three time points (age 18 years, year 1976, and current) were derived from the reported height (1976) and corresponding reported weight. Weight changes between age 18 years and 1976 and after diagnosis of diabetes were calculated. Women reported diagnoses of diabetes and CHD every 2 years. Incident CHD cases were confirmed by medical record review.

RESULTS — During follow-up, we documented 418 incident cases of CHD (236 of nonfatal myocardial infarction and 182 of fatal CHD). After adjustment for age, smoking, and other coronary risk factors, current BMI was strongly associated with increased risk of CHD among diabetic women. The multivariate relative risks across increasing categories of BMI (<23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2) were 1.0, 1.58, 1.85, 1.95, 2.80, and 3.21, respectively (P for trend <0.001). Increasing BMI values from age 18 years to 1976, before diagnosis of diabetes, were also positively associated with risk of CHD. Weight gain before the diagnosis of diabetes was related to increased risk of CHD. In contrast, weight change after diagnosis of diabetes was not associated with risk of CHD.

CONCLUSIONS — These findings provide strong evidence that obesity and weight gain before diagnosis of diabetes are associated with future risk of CHD among women with type 2 diabetes.

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Coronary heart disease (CHD) is a leading cause of death among people with type 2 diabetes. Diabetes substantially increases risk of both nonfatal myocardial infarction (MI) and fatal CHD, especially in women (1,2), and negates the usual protection conferred by female sex against CHD (3).

Obesity is a well-established predictor of CHD in the general population (4,5). Surprisingly, in most studies of individuals with diabetes, a positive association was not found between obesity and CHD death or total mortality (6–17). Small sample size and relatively short follow-up may account for these null associations. Although weight gain is an independent risk factor for CHD (4,5), the association between weight change and risk of CHD has not been well defined in diabetic populations (16).

Because obesity is highly prevalent among people with type 2 diabetes and weight control is a cornerstone of diabetes management, it is important to understand the relationship of obesity and weight change to risk of CHD among diabetic individuals. Therefore, we evaluated the impact of obesity and weight change on subsequent risk of CHD among diabetic women in the Nurses' Health Study (NHS).

RESEARCH DESIGN AND METHODS

— The NHS was established in 1976, when 121,700 female registered nurses, aged 30–55 years and living in 1 of 11 U.S. states, returned a mailed questionnaire regarding their medical histories and lifestyles. Follow-up questionnaires have since been sent every 2 years to ascertain the incidence of such diseases as MI, diabetes, hypercholesterolemia, and hypertension and to update information on lifestyle factors.

For the present study, we followed women who provided information on both height and weight in 1976 and reported a physician's diagnosis of diabetes at ≥40 years of age (a working definition for type 2 diabetes). Among them, we excluded women with a history of cardiovascular disease (including MI, angina, coronary revascularization, and/or stroke) and/or cancer (except nonmelanoma skin cancer) in 1976. For women in whom diabetes was diagnosed after 1976, we excluded those who had developed cardiovascular disease or cancer before or at the time of diabetes diagnosis. Therefore, none of our cohort members had diagnosed cardiovascular disease or cancer at the beginning of the follow-up period.

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Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; NHS, Nurses' Health Study; RR, relative risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

A total of 5,897 diabetic women comprised the analytic cohort: 1,310 women reported a diabetes diagnosis on the 1976 questionnaire and 4,587 women reported this diagnosis during follow-up through 1994.

Measures of obesity, weight change, and other risk factors for CHD

Nurses have provided their current personal information regarding age, weight, smoking status, postmenopausal hormone use, and physician-diagnosed hypertension and high blood cholesterol biennially since 1976. Information regarding current height and parental history of MI before 60 years of age was collected in 1976. The 1980 questionnaire asked about weight at 18 years of age; ~80% of the participants provided the information. Information on physical activity was collected in 1980, 1982, 1986, 1988, and 1992. We created a variable representing the average number of hours per week spent at moderate/vigorous recreational activities over these years. Diet was assessed using validated semiquantitative food-frequency questionnaire in 1980, 1984, 1986, 1990, and 1994 (18). The 1988 and 1994 main questionnaires included items concerning use of insulin or oral diabetic medication. The 1992 questionnaire asked about major ancestry of the nurses. Our cohort included only 3.3% minorities (2% African-Americans, 0.5% Hispanics, and 0.8% Asians).

As a measure of obesity, we calculated BMI as weight in kilograms divided by the square of height in meters (kg/m^2). We derived three different BMI variables: BMI at 18 years of age, BMI in 1976, and current BMI (updated biennially) calculated using height reported in 1976 and weight corresponding to each time. We used weight changes (kg) between 18 years of age and 1976 to predict incidence of CHD among women in whom diabetes was diagnosed after 1976. For these women, we also calculated weight change after diagnosis of diabetes (difference between weight before diagnosis of diabetes and current weight).

Self-reported weights were validated in a subsample of 184 NHS participants living in the Boston, MA area and were highly correlated with actual measured weights ($r = 0.96$, mean difference [self-reported weight – actual measured weight] = −1.5 kg) (19). Recalled weight at 18 years of age was also highly correlated ($r = 0.87$, mean difference [recalled weight – measured weight] = −1.4 kg) with measured weight from the physical examination records for the same age in a subsample of 118 women from another cohort of female nurses aged 25–42 years (20).

Documentation of diabetes

When a participant reported a diagnosis of diabetes, we mailed her a supplementary questionnaire requesting information on details of diagnosis (i.e., diagnostic tests, symptoms, and year of diagnosis) and therapy (insulin or oral hypoglycemic treatment). A diabetes case was considered confirmed if at least one of the following was reported on the supplementary questionnaire: *1*) one or more classical symptoms (excessive thirst, polyuria, unexplained weight loss, hunger, and pruritus) plus a fasting plasma glucose level of ≥140 mg/dl (7.8 mmol/l) or a random plasma glucose level of ≥200 mg/dl (11.1 mmol/l); *2*) at least two elevated plasma glucose concentrations on different occasions (a fasting level of ≥140 mg/dl or a random level of ≥200 mg/dl, and/or a concentration of ≥200 mg/dl after ≥2 h of oral glucose tolerance testing) in the absence of symptoms; or *3*) treatment with hypoglycemic medications (insulin or oral hypoglycemic agents).

To document the validity of self-reported diabetes, we obtained medical records for a random sample of women reporting a diabetes diagnosis (2). Among 84 women classified by the questionnaire as having type 2 diabetes, 71 women provided permission to review their medical records and records were available for 62 women. An endocrinologist blinded to the information reported on the supplementary questionnaire reviewed the records according to the National Diabetes Data Group criteria (21). The diagnosis of type 2 diabetes was confirmed in 61 (98%) of the 62 women (2). Secondary analyses including only cases of type 2 diabetes confirmed by the supplementary questionnaire ($n = 4,423$) yielded similar results.

Documentation of CHD

Nonfatal MI and fatal CHD that occurred between the return of the 1976 questionnaire and 1 June 1996 were considered end points. If a participant reported a diagnosis of nonfatal MI, we requested permission to review her medical records. Study physicians who were unaware of the women's risk factor status reviewed the records to confirm the diagnosis using World Health Organization criteria (22): the presence of compatible symptoms plus either typical electrocardiographic changes or elevations of serum cardiac enzyme levels. Infarctions were classified as probable if a patient required hospital admission, and confirmatory information was obtained by interview or letter from the patient without medical records. We included all confirmed ($n = 191$) and probable ($n = 45$) cases of nonfatal MI in our analyses.

Deaths were identified from state vital records and the National Death Index or were reported by next of kin and the postal system. Follow-up for the deaths was >98% complete. Fatal coronary disease was defined as fatal MI if this diagnosis was confirmed by hospital records or autopsy or if coronary disease was listed as the cause of death on the death certificate and evidence of previous coronary disease was available. We designated as presumed fatal CHD those cases in which CHD was the underlying cause on the death certificate but no records were available. These cases ($n = 37$) constituted 20% of fatal CHD cases ($n = 182$). Also included under this designation were cases of sudden death (within 1 h of onset of symptoms) with no plausible explanation other than coronary disease ($n = 14$). Analyses limited to confirmed cases yielded similar results, although with less precision.

Statistical analysis

We calculated incidence rates of CHD according to categories of BMI and weight change. Participants contributed person-time from the date of return of the 1976 questionnaire (for prevalent diabetics) or from the date of diabetes diagnosis (for incident diabetics) until the date of occurrence of CHD, the date of death, or 1 June 1996, whichever came first. The relative risk (RR) was calculated as the rate for a given category of BMI or weight change as compared with the referent category. Age-adjusted analyses were conducted using 5-year age categories. Pooled logistic regression was used to adjust for age or other potential confounders, including smoking, menopausal status/postmenopausal hormone use, parental history of MI before 60 years of age, duration of di-

Table 1—*Age-adjusted characteristics of diabetic women in 1986 according to BMI in 1986**

	BMI (kg/m^2)					
	<23	23.0–24.9	25.0–26.9	27.0–29.9	30.0–34.9	≥35.0
N in 1986	633	444	473	689	847	593
Mean age (years)	54	54	56	55	55	54
Mean weight gain from 18 years of age to 1986 (kg)	3	7	11	14	19	27
Current smoking (%)	32	26	23	20	17	13
Current use of postmenopausal hormone (%)	14	14	11	10	8	5
History of hypertension (%)	32	42	51	59	67	77
History of high blood cholesterol (%)	22	25	27	28	29	28
Mean duration of diabetes (years)	13	11	10	9	8	7
Use of insulin (%)†	48	38	38	33	35	35
Use of Oral hypoglycemic medication (%)†	19	31	38	42	52	52
Parental history of myocardial infarction before 60 years of age (%)	20	25	24	25	24	24

*Except for the data on mean age, all data shown are standardized to the age distributions of the cohort in 1986 (we used 1986 to represent overall follow-up period); †information collected in 1988 and from diabetes supplementary questionnaire was used.

abetes, and insulin or other hypoglycemic treatment use simultaneously. It has been shown that the pooled logistic regression is asymptotically equivalent to the Cox proportional hazard regression with time-varying covariates (23). The necessary conditions for this equivalence include relatively short time intervals and small probability of the outcome in the intervals, both of which are satisfied here. The categorization of the covariates is provided in the last footnote to Table 2. Age, smoking, menopausal status/postmenopausal hormone use, and duration of diabetes were updated at 2-year intervals. In secondary analyses using 1980 as baseline, we also adjusted for physical activity levels (<1, 1.0–1.9, 2.0–3.9, 4.0–6.9, and ≥7.0 h of exercise per week), alcohol use (0, 0.1–4.9, 5.0–14.9, and ≥15 g/day), total dietary fat, folate, fiber (all in quintiles), and vitamin E supplement use (yes or no). For all RRs, 95% CIs were calculated. Tests for trend were conducted using the median value for each category of BMI or weight change as a continuous variable. All *P* values were two-sided.

RESULTS — During 57,909 person-years of follow-up of 5,897 diabetic women (1,310 prevalent and 4,587 incident diabetic cases), we documented 418 incident cases of CHD (236 nonfatal MI and 182 fatal CHD). The characteristics of these diabetic women according to BMI categories as of 1986 are shown in Table 1. We used 1986 in this analysis because it included both incident and prevalent diabetic cases and represented the midpoint of the follow-up period. Women with greater BMI in 1986 tended to have gained more weight between 18 years of age and 1986. Greater BMI was inversely associated with smoking and postmenopausal hormone replacement therapy and positively associated with a history of hypertension. In particular, the prevalence of hypertension ranged from 32% in diabetic women with BMI <23 kg/m^2 to 77% in those with BMI ≥35 kg/m^2. Use of oral hypoglycemic medication also increased with BMI, ranging from 19 to 52%. Leaner diabetic women were more likely to have a longer duration of diabetes.

Risk of CHD increased monotonically with increasing current BMI. Compared with diabetic women with BMI <23.0 kg/m^2, those with BMI 25.0–26.9 kg/m^2 had a multivariate RR of 1.85 (95% CI 1.18–2.88) for CHD, and those with BMI ≥35.0 kg/m^2 had a more than threefold higher risk of the disease (Table 2). The multivariate RR for each 1-unit increase of BMI was 1.05 (1.03–1.07). BMI in 1976 and at 18 years of age were also significantly associated with elevated risk of CHD in women with diabetes. The multivariate RRs for each 1-unit increase of BMI in 1976 and BMI at 18 years of age were 1.06 (1.05–1.08) and 1.07 (1.05–1.10), respectively.

For the purpose of comparison, we also conducted analyses among nondiabetic women in our cohort of nurses. The multivariate RRs across increasing categories of current BMI (<23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2) were 1.00, 1.14, 1.23, 1.70, 1.88, and 2.44 (*P* for trend <0.001).

The above analyses included both women with prevalent diabetes in 1976 and those with incident diabetes developing during follow-up (1976–1994). Because BMI in 1976 among those who were already diabetic at that time may have been affected by existing disease or medications, we conducted separate analyses for prevalent and incident cases of diabetes. The positive association between BMI at three different time points and risk of CHD was evident among both prevalent and incident diabetic cases.

Because hypertension and high blood cholesterol are considered intermediate variables in the causal pathway between obesity and CHD, we did not adjust for these variables in the primary analyses. However, further adjustment for history of hypertension and high blood cholesterol did not substantially alter the results. For example, the RR for CHD associated with the highest category of current BMI was only modestly attenuated after adjustment for these variables (BMI ≥35 vs. <23 kg/m^2 = 2.72 [1.79–4.12, *P* for trend <0.001]). In 1990, we asked the nurses to report serum cholesterol levels (range <140 to ≥ 330 mg/dl). Additional analysis using 1990 as the baseline and adjusting for reported serum cholesterol levels yielded similar results.

The strong positive association between BMI and risk of CHD was observed for both nonfatal MI and fatal CHD. Compared with women with a current BMI <23 kg/m^2, the RR among women with BMI ≥35.0 kg/m^2 was 3.39 (1.92–5.99)

Table 2—*RR of CHD among diabetic women according to BMI

	BMI (kg/m^2)							
	<20	20.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–34.9	≥35.0	*P* for trend†
Current BMI (updated every 2 years)								
N		35	38	47	77	129	92	
Age-adjusted		1.00	1.43 (0.90–2.26)	1.61 (1.04–2.51)	1.70 (1.14–2.55)	2.42 (1.66–3.52)	2.73 (1.84–4.06)	<0.001
Multivariate‡		1.00	1.58 (0.99–2.52)	1.85 (1.18–2.88)	1.95 (1.30–2.95)	2.80 (1.90–4.13)	3.21 (2.13–4.84)	<0.001
Multivariate (among incident diabetic women: *n* = 229 cases of CHD)		1.00	2.31 (1.11–4.80)	2.17 (1.06–4.45)	2.43 (1.24–4.75)	2.91 (1.52–5.59)	4.17 (2.15–8.12)	<0.001
Multivariate (among prevalent diabetic women: *n* = 189 cases of CHD)		1.00	1.12 (0.59–2.13)	1.70 (0.94–3.07)	1.67 (0.97–2.88)	3.10 (1.90–5.07)	2.44 (1.40–4.27)	<0.001
BMI in 1976 (study entry)								
N		40	41	42	80	137	78	
Age-adjusted		1.00	1.32 (0.85–2.04)	1.49 (0.96–2.30)	1.82 (1.24–2.66)	2.95 (2.07–4.21)	3.13 (2.13–4.60)	<0.001
Multivariate‡		1.00	1.53 (0.98–2.38)	1.68 (1.08–2.62)	2.02 (1.37–2.99)	3.26 (2.26–4.71)	3.43 (2.30–5.11)	<0.001
Multivariate (among incident diabetic women: *n* = 229 cases of CHD)		1.00	2.02 (0.99–4.12)	1.89 (0.94–3.80)	2.27 (1.19–4.34)	3.82 (2.04–7.12)	4.44 (2.31–8.53)	<0.001
Multivariate (among prevalent diabetic women: *n* = 189 cases of CHD)		1.00	1.21 (0.67–2.19)	1.60 (0.87–2.94)	1.99 (1.19–3.33)	3.12 (1.95–4.99)	2.77 (1.61–4.77)	<0.001
BMI at 18 years of age								
N	62	101	69	56		45		
Age-adjusted	1.00	1.19 (0.87–1.64)	1.78 (1.26–2.52)	1.78 (1.24–2.57)		3.90 (2.64–5.78)		<0.001
Multivariate‡	1.00	1.15 (0.84–1.58)	1.63 (1.15–2.32)	1.51 (1.04–2.19)		3.06 (2.05–4.55)		<0.001
Multivariate (among incident diabetic women: *n* = 190 cases of CHD)	1.00	1.18 (0.77–1.81)	1.62 (1.01–2.58)	1.61 (0.99–2.60)		2.90 (1.66–5.05)		<0.001
Multivariate (among prevalent diabetic women: *n* = 144 cases of CHD)	1.00	1.16 (0.71–1.88)	1.64 (0.97–2.77)	1.45 (0.81–2.59)		3.22 (1.80–5.75)		<0.001

*Data are RR (95% CI). Prevalent diabetic cases are women with existing diabetes in 1976, and incident diabetic cases are women who developed diabetes between 1976 and 1994; †*P* value, test for trend; ‡adjusted for age (5-year categories), smoking (never, past, current 1–14, current 15–24, current 25+ cigarettes per day), use of postmenopausal hormone (premenopausal, never, past, current), parental history of myocardial infarction before 60 years of age (yes or no), duration of diabetes (≤5, 6–10, 11–15, ≥15 years), insulin or other hypoglycemic treatment usage (no, oral medication only, insulin and/or oral medication), and time period (10 periods).

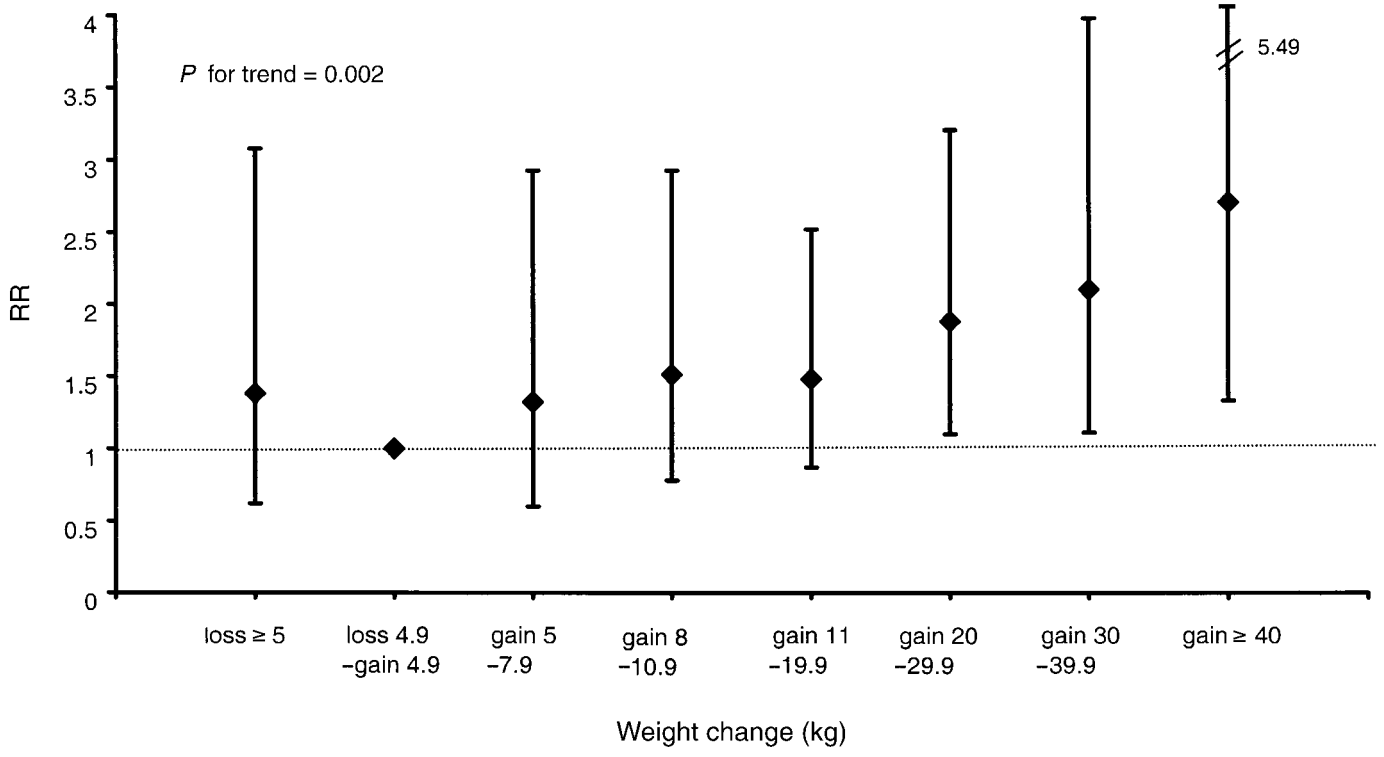

Figure 1—*Multivariate RR of CHD among women with incident diabetes by weight change between 18 years of age and 1976. The model was adjusted for BMI at 18 years of age as well as the covariates listed in Table 2.*

for nonfatal MI and 2.83 (1.57–5.11) for fatal CHD.

Because the BMI values at three different time points were correlated, we examined the joint effects of these variables on risk of CHD. We restricted these analyses to incident cases of diabetes only. Women with BMI >23 kg/m^2 at 18 years of age and BMI >30 kg/m^2 in 1976 had a relative risk of 3.15 (1.93–5.14) compared with women with BMI <23 kg/m^2 at 18 years of age and <25 kg/m^2 in 1976. Women who were overweight (BMI ≥25 kg/m^2) in 1976 and currently obese (BMI ≥30 kg/m^2) had a RR of 2.50 (1.53–4.07) compared with women who were not overweight (BMI <25 kg/m^2) at either time point.

Because information on important potential confounders such as physical activity and dietary intake was first collected in 1980, we repeated the analysis using only cases diagnosed after this time and obtained similar results. Adjustment for physical activity levels only slightly attenuated the results: the RR comparing current BMI ≥35 kg/m^2 to <23 kg/m^2 changed from 3.22 (2.13–4.87) to 3.15 (2.08–4.76). Further adjustment for alcohol use and dietary intakes of total fat, fiber, folate, and vitamin E did not appreciably alter the results. Because of the small number of minorities in this cohort, we were not able to conduct separate analyses among minority groups. Further analyses adjusting for race or excluding minorities did not alter the results.

Weight gain before the diagnosis of diabetes (from 18 years of age to 1976) was significantly associated with future risk of CHD (Fig. 1). Compared with women with stable weight (gain or loss <5 kg), the RRs for CHD were 1.88 (1.10–3.21) for a gain of 20–29.9 kg, 2.10 (1.11–3.98) for a gain of 30–39.9 kg, and 2.71 (1.33–5.49) for a gain of ≥40 kg among incident diabetes cases, in a multivariate analysis accounting for BMI at 18 years of age and other potential confounders. For comparison, we conducted analyses among nondiabetic women in our cohort; the multivariate RRs for the same categories (loss ≥5.0, loss 4.9–gain 4.9, gain 5.0–7.9, gain 8.0–10.9, gain 11.0–19.9, gain 20.0–29.9, gain 30.0–39.9, and gain ≥40.0 kg) of weight change between 18 years of age and 1976 were 0.80, 1.00, 1.06, 1.36, 1.57, 1.87, 1.88, and 4.37 (*P* for trend <0.001).

Weight change after the diagnosis of diabetes did not seem to be strongly related to CHD risk among incident diabetic women with updated weight information. A total of 171 cases of CHD occurred among them. Compared with women with weight change ≤2 kg, those who gained ≥2 kg after diabetes diagnosis had a RR of 1.16 (0.75–1.78) and those who lost 2–10.9 kg and ≥11 kg had RRs of 0.98 (0.64–1.51) and 0.87 (0.49–1.55), respectively, in multivariate analysis that adjusted for BMI in 1976 and other risk factors. In this analysis, we used a smaller change of weight as a reference because of a small number of cases. Further analyses excluding insulin users (because insulin may affect body weight) yielded similar results (data not shown).

CONCLUSIONS — This prospective study provides strong evidence that obesity increases future risk of CHD in diabetic women. In addition, weight gain before the diagnosis of diabetes strongly predicts future risk of CHD in individuals with diabetes.

Obesity is a well-established risk factor for CHD in the general population (4,5), but studies of diabetic cohorts have yielded inconsistent results (6–17). Of

these published studies, only a few documented direct, positive relationships between obesity and mortality from all causes or from cardiovascular disease. Ross et al. (17) followed 373 patients with type 2 diabetes for 14 years and found a J-shaped association between BMI and all-cause mortality, but there was no clear association between BMI and CHD mortality. In the National Health and Nutrition Examination Survey 1 Epidemiologic Follow-up Study, obesity was significantly related to increased CHD mortality among individuals with type 2 diabetes (12). In the London cohort of the World Health Organization Multinational Study of Vascular Disease in Diabetics, increasing BMI was related to increased risk of cardiovascular mortality in individuals with type 2 diabetes (11). However, other studies did not find a significant overall association between obesity and CHD mortality in individuals with diabetes (6–10,13,14,16). Most of the previous studies had relatively small sample sizes (n <1,000) with limited information on confounding variables. In addition, most studies did not distinguish type 1 and type 2 diabetes and did not exclude preexisting CHD or cancer, which may affect BMI and obscure the true association between obesity and coronary risk.

The mechanisms through which obesity affects CHD risk in individuals with diabetes are likely to be multiple. Obesity is a powerful risk factor for hypertension. It adversely affects blood lipid profiles (increasing triglycerides and decreasing HDL cholesterol) and increases oxidative stress (24,25). It also decreases fibrinolysis, increases erythrocyte aggregation, and induces endothelial dysfunction (26–28). Acute-phase C-reactive protein, a marker of systemic inflammation and a significant predictor of CHD, was increased in overweight individuals (29). Among those with diabetes, obesity may aggravate glucose intolerance, hyperinsulinemia, and insulin resistance (30,31). Several studies have reported that moderate weight loss improves cardiovascular risk profiles such as glycemic control, insulin sensitivity, blood pressure, and blood cholesterol in obese patients with type 2 diabetes (10,32,33).

In our study, weight gain before diagnosis of diabetes seemed to be strongly related to CHD. However, neither gain nor loss of weight after diagnosis of diabetes was significantly associated with risk of CHD. It is possible that after development of diabetes, insulin resistance is so great that any additional weight gain may not confer further increase of cardiovascular risk. In this analysis, however, our power was limited because the analysis was limited to individuals with incident diabetes and updated weight information. Furthermore, the effects of weight change on CHD in diabetic individuals are difficult to evaluate in observational settings. The benefit of intentional weight loss could be confounded by unintentional weight loss due to severity of diabetes. In addition, weight loss may reflect poorer control of diabetes; higher blood glucose levels promote urinary glucose loss and, subsequently, caloric loss. Weight gain may also occur due to insulin or other hypoglycemic treatment such as sulfonylurea. Although we included use of diabetic medication and duration of diabetes in the models to adjust for severity of diabetes and potential effects of diabetes treatment on body weight, such adjustment may not be adequate. In addition, we had limited information on intentional weight loss and were not able to examine weight cycling. Finally, considering that weight loss is more frequently seen in type 1 diabetes, there is a possibility of misclassification of type 2 with type 1 diabetes. To avoid this, we included only women who reported a diagnosis of diabetes at ≥40 years of age. Moreover, the analysis restricted to confirmed type 2 diabetic cases by the supplementary questionnaire yielded similar results.

The power of this study was greatly enhanced by the large number of diabetic cases and the long follow-up periods. In addition, because body weight was assessed every 2 years during the study period, we were able to examine the relationship between obesity at different time points (at 18 years of age as well as before and after the diagnosis of diabetes) and risk of CHD. Validation studies have confirmed the reliability of self-reported weight (19,20). Although BMI may not be a perfect measure of true adiposity, the resulting random misclassification would tend to underestimate the true association between adiposity and CHD. In addition, we collected detailed information on a wide range of cardiovascular risk factors, including diet and physical activity. The strong positive associations remained after adjusting for these variables, suggesting that confounding by these variables was an unlikely explanation for our findings. Although we did not have direct measures of glycemic control such as HbA_{1c}, we adjusted for duration of diabetes, a good marker of severity of the disease and a strong predictor of CHD in this diabetic population. Because most of our participants were white, our findings may not be generalized to other racial groups. Also, these results need to be confirmed in diabetic men.

In our analysis, we used the National Diabetes Data Group criteria (21) because all of the diabetic patients were diagnosed before 1996, before the release of the criteria (34) from the American Diabetes Association. According to the new criteria, some women who were not considered to have diabetes by old standards would now be considered to have this diagnosis. However, this would not affect the case status of the women included in the present analyses.

In conclusion, in this population of women with type 2 diabetes, obesity is associated with substantially increased risk of CHD. Our results also suggest that weight gain before diagnosis of diabetes predicts future risk of CHD among diabetic women. The benefits of weight loss after diagnosis of diabetes need to be studied in the settings of an experimental study.

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