Adiposity Compared With Physical Inactivity and Risk of Type 2 Diabetes in Women

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OBJECTIVE — The relative contribution of adiposity and physical inactivity to the risk of developing type 2 diabetes remains controversial.

RESEARCH DESIGN AND METHODS — We prospectively examined the individual and joint association of obesity and physical activity with the development of type 2 diabetes in 68,907 female nurses who had no history of diabetes, cardiovascular disease, or cancer at baseline. Adiposity was measured by BMI and waist circumference. Physical activity was assessed through average hours of moderate or vigorous exercise and computation of an MET score.

RESULTS — We documented 4,030 incident cases of type 2 diabetes during 16 years of follow-up (from 1986 to 2002). In a multivariate model including age, smoking, and other diabetes risk factors, risk of type 2 diabetes increased progressively with increasing BMI ($P < 0.001$) and waist circumference ($P < 0.001$) and with decreasing physical activity levels ($P < 0.001$). In joint analyses of BMI and physical activity, using women who had a healthy weight (BMI <25 kg/m^2) and were physically active (exercise ≥21.8 MET h/week) as the reference group, the relative risks of type 2 diabetes were 16.75 (95% CI 13.99–20.04) for women who were obese (BMI ≥30 kg/m^2) and inactive (exercise <2.1 MET h/week), 10.74 (8.74–13.18) for women who were active but obese, and 2.08 (1.66–2.61) for women who were lean but inactive. In combined analyses of waist circumference and physical activity, both variables were significant predictors of type 2 diabetes, but the association for waist circumference was substantially stronger than that for physical inactivity.

CONCLUSIONS — Obesity and physical inactivity independently contribute to the development of type 2 diabetes; however, the magnitude of risk contributed by obesity is much greater than that imparted by lack of physical activity.

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Type 2 diabetes is a major cause of morbidity and mortality and has become an important public health issue worldwide (1). Obesity and physical inactivity are well-known risk factors for the development of type 2 diabetes (2–6). It has been suggested that higher levels of physical activity can mitigate the impact of overweight and obesity on morbidity and mortality, and, thus, obesity may not be detrimental to those who are physically fit (7). However, our recent analyses indicated that both obesity and physical activity were independent predictors of all-cause mortality (8) and coronary heart disease (9), and being physically active did not abolish the excess risk associated with obesity. For type 2 diabetes, a recent study (10) suggested that the magnitude of association with BMI was much greater than that with physical inactivity and that physical activity was less predictive of diabetes in overweight and obese individuals than in those with normal weight. In addition, a recent Finnish study (11) showed that increasing physical activity was associated with a significantly reduced risk for type 2 diabetes, especially in obese patients. In this study, we evaluated the individual and combined association of obesity and physical inactivity with the incidence of type 2 diabetes among 68,907 participants in the Nurses' Health Study.

RESEARCH DESIGN AND METHODS

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire about their medical history and lifestyle. Women have provided information regarding lifestyle and health conditions biennially since 1976. The 1980 questionnaire asked about weight at 18 years of age; ~80% of the participants provided the information. Diet and physical activity were assessed by validated questionnaires starting from 1980 (12). For this study, we included 68,907 women in the analyses after excluding those who reported cardiovascular disease, diabetes, or cancer at baseline in 1986. We chose 1986 as the baseline since we had more detailed information regarding physical activity and waist circumference along with BMI. The study was approved by the Human Research Committees at the Brigham and Women's Hospital.

Assessment of overall and abdominal adiposity

BMI was calculated as weight in kilograms divided by the square of height in meters to assess overall obesity. Self-reported weights were validated among 184 participants in the Nurses' Health Study living in the Boston area and were highly correlated with measured weights ($r = 0.96$, mean difference [self-reported − measured weight] = −1.5 kg) (13).

In 1986, Nurses' Health Study participants measured and reported measurements of their waist (at the umbilicus) and hip (the largest circumference) to the near-

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

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est quarter of an inch. In a validation study, the correlation between self-reported and technician-measured circumferences was 0.89 for the waist (14). We had information on waist circumference on 63.8% of the participants followed.

Assessment of physical activity

In 1986, 1988, 1992, 1996, 1998, and 2000, women were asked to report the average time spent per week on the following activities: walking, jogging, running, bicycling, lap swimming, playing tennis or squash, and participating in calisthenics. Using this information, we calculated the average amount of time per week spent in moderate-to-vigorous activities (requiring three or more METs per hour, including brisk walking) at each time point (15). We divided physical activity by quintiles such that the current physical activity recommendation of ≥150 min or 10 MET h/week of moderate-intensity physical activity was met by women in the fourth and fifth quintiles. Our validation study indicated relatively good validity and reproducibility for the questionnaire. The correlation between physical activity reported on 1-week recalls and that reported on the questionnaire was 0.79. The correlation between moderate-to-vigorous activity reported in diaries and that reported on the questionnaire was 0.62.

Walking, a moderate-intensity activity, was by far the most prevalent physical activity in our cohort. In 1986, women were also asked about their usual walking pace, specified as easy (<3.2 km/h) or normal (3.2–4.8 km/h). Because only 2% of women reported a very brisk (≥6.4 km/h) pace, we combined it with the brisk (4.8–6.2 km/h) category in the analyses of walking pace. For this information, weekly walking energy expenditure in MET hours was calculated to differentiate between moderate and vigorous activity (16).

Ascertainment of end point

The primary end point for this study was type 2 diabetes. At each 2-year questionnaire cycle, participants were asked whether they had a diagnosis of diabetes. For each self-reported diagnosis of diabetes, a supplemental questionnaire was sent asking about diabetes symptoms, diagnostic tests, and treatments. A diagnosis of diabetes was made when any one of the following criteria were met: *1*) one or more classic symptoms of diabetes and elevated plasma glucose levels (fasting plasma glucose 7.8 mmol/l or randomly measured plasma glucose 11.1 mmol/l), *2*) elevated plasma glucose on at least two occasions in the absence of symptoms, or *3*) treatment with oral hypoglycemic medication or insulin. Our criteria for the diagnosis of diabetes are consistent with those proposed by the National Diabetes Data Group (17) for cases that were diagnosed before 1997. For diagnoses of diabetes established after 1998, the new American Diabetes Association criteria (fasting plasma glucose ≥7 mmol/l) were used. We excluded women with type 1 diabetes or gestational diabetes. The diagnosis of type 2 diabetes by the use of the supplemental questionnaire has been validated (5).

Statistical analysis

We grouped women into nine categories of BMI measured in 1986, which included standard cutoffs for overweight (BMI ≥25 kg/m^2), class 1 obesity (BMI ≥30 kg/m^2), class 2 obesity (BMI ≥35 kg/m^2), and class 3 obesity (BMI ≥40 kg/m^2). Participants contributed person-time from the date they returned the 1986 questionnaires (BMI and waist circumference analyses) until the date of death or June 1, 2002, whichever came first. The relative risk (RR) was calculated as the rate for a given category of BMI compared with the referent category. Age-adjusted analyses were conducted using 5-year age categories by the Mantel-Haenszel method. Cox proportional hazard regression was used to adjust for age or other potential confounders, including smoking status (never; past; or current smoker of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 1–4, 5–14, or ≥15 g/day), menopausal status and postmenopausal hormone use, and parental history of diabetes. Analysis of BMI and risk of type 2 diabetes was additionally adjusted for physical activity in five categories.

To best represent long-term physical activity levels and to reduce measurement error, we created measures of cumulative average of hours of moderate-to-vigorous activities from all available questionnaires up to the start of each 2-year follow-up interval (18). In a secondary analysis, we also controlled for a dietary score reflecting high intakes of the ratio of polyunsaturated fat to saturated fat, cereal fiber, low intakes of trans fat, and glycemic load (19). We examined the joint associations of physical activity and BMI and waist circumference with risk of type 2 diabetes. Statistical analyses were conducted using SAS version 8.2 (Cary, NC). All *P* values were two sided.

RESULTS — During 16 years of follow-up from 1986 to 2002, 4,030 incident cases of type 2 diabetes were identified. Table 1 shows RRs of type 2 diabetes according to BMI categories at baseline in 1986. The risk of type 2 diabetes increased progressively with increasing BMI. Women with BMI ≥40 kg/m^2 had an ~28-fold higher risk of type 2 diabetes than those with BMI <21 kg/m^2. Similarly, the risk of type 2 diabetes increased progressively with increasing quintiles of waist circumference (*P* for trend <0.001). Further adjustment for dietary score did not change the association.

We assessed physical activity according to the intensity and amount of exercise (MET hours per week). There was a progressive increment in the multivariable-adjusted RR of diabetes with decreasing quintiles of total MET hours per week (Table 2). This inverse gradient, although attenuated, still remained statistically significant after adjustment for BMI (RRs across quintiles were 1.66, 1.56, 1.30, 1.27, and 1.0, respectively; *P* for trend <0.001).

In Table 3, we present joint associations of BMI and physical activity with the risk of type 2 diabetes. Both higher BMI and lower physical activity levels were associated with increased risk of type 2 diabetes (*P* for interaction was 0.22 between physical activity and BMI). Compared with women who were physically active and had a BMI <25 kg/m^2, women who were lean but physically inactive had an RR for type 2 diabetes of 2.08 (95% CI 1.66–2.61). Obese women (BMI ≥30 kg/m^2) who were physically active had an RR of 10.74 (8.74–13.18), and obese women who were inactive had an RR of 16.75 (13.99–20.04). Thus, increasing BMI in the same category of physical activity markedly increased the risk for type 2 diabetes. Even in the physically active group, the RR increased 11-fold in obese participants compared with lean participants. Further adjustment for dietary score did not appreciably alter these results.

In joint analyses of physical activity and abdominal adiposity, the highest risk of type 2 diabetes was among women in the lowest category of physical activity and the highest tertile of waist circumference (RR 22.26 [95% CI 15.75–31.45]). The associations of physical activity and abdominal obesity with type 2 diabetes were independent of each other (*P* for interaction was 0.85 between physical ac-

Table 1—*Baseline BMI, waist circumference, and RR of type 2 diabetes in the Nurses' Health Study from 1986 through 2002*

	BMI (kg/m^2) (n = 68,907)							
	<21	21–22.9	23–24.9	25–26.9	27–29.9	30–32.9	33–34.9	35–39.9	40	*P* for trend
n	95	224	438	555	944	730	328	482	234	
Person-years (1,034,808)	165,274	229,913	224,553	150,502	137,714	67,443	22,615	26,277	10,567	
Age-adjusted RR (95% CI)	1.00	1.68 (1.32–2.13)	3.32 (2.66–4.14)	6.26 (5.04–7.79)	11.67 (9.45–14.41)	18.62 (15.04–23.07)	25.31 (20.14–31.81)	32.56 (26.12–40.57)	40.28 (31.73–51.13)	<0.001
Multivariate RR (95% CI)*	1.00	1.65 (1.30–2.10)	3.10 (2.48–3.87)	5.51 (4.43–6.86)	9.80 (7.93–12.11)	14.83 (11.96–18.39)	19.11 (15.19–24.06)	23.98 (19.21–29.95)	27.96 (21.97–35.58)	<0.001
	Waist circumference (inches) (n = 43,986)									
	20–28	28–29.9	30–31.9	32–34.9	≥35	*P* for trend				
n	58	156	248	584	1,096					
Person-years (664,976)	149,922	156,197	125,540	131,638	101,633					
Age-adjusted RR (95% CI)	1.00	2.55 (1.89–3.45)	5.03 (3.78–6.69)	11.25 (8.58–14.75)	27.69 (21.24–36.09)	<0.001				
Multivariate RR (95% CI)*	1.00	2.48 (1.83–3.35)	4.62 (3.47–6.15)	9.51 (7.25–12.47)	21.44 (16.42–28.00)	<0.001				

*Adjusted for age (<49, 50–54, 55–59, 60–64, and 65 years), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), family history of diabetes, postmenopausal status and hormone use (pre- and postmenopausal status and hormone use as never, past, or current), physical activity (quintiles), and alcohol consumption (0, 0.1–4.9, 5–14.9, or 15 g/day).

tivity and waist circumference). Further adjustment for BMI attenuated these results, but the increased risk associated with abdominal obesity remained significant (Table 3).

We also examined the combined association of BMI with walking pace among the women (n = 47,358) who did not perform vigorous exercise. When we compared the pace of the moderate-intensity physical activity of walking, we found that slower pace of walking was associated with higher risk of diabetes within the same BMI category (Fig. 1). The inverse association between pace and intensity of walking and risk of diabetes was most evident in overweight and obese patients. Among overweight women, slower pace was associated with nearly double the risk of developing type 2 diabetes compared with brisk or very brisk pace.

CONCLUSIONS — In this large prospective cohort, we found that obesity and physical inactivity independently contributed to the development of type 2 diabetes. The magnitude of risk contributed by obesity appeared to be much greater than the risk imparted by physical inactivity.

Data on the relative influence of obesity and physical inactivity on risk of development of diabetes are sparse and controversial (10,11,20). A recent study (10) indicated that physical activity had relatively small effects on diabetes in overweight and obese patients. The Medical Expenditure Panel Survey (20) showed that inactive normal weight individuals had lower risk than obese and active individuals. However, due to the cross-sectional nature of the data, any temporal effect of activity versus obesity on risk of type 2 diabetes could not be demonstrated; whereas a Finnish study (11) showed that increasing physical activity was associated with a significantly reduced risk for type 2 diabetes, especially in obese patients.

Our study had several strengths. We had a much larger sample size and a longer follow-up. We assessed both obesity and physical activity in several ways. For adiposity, we examined both overall obesity and central obesity. For physical activity, we assessed both the amount and intensity of activity according to MET hours per week. Finally, we examined the most common form of exercise, walking (20), and the relative effect of its intensity or pace versus adiposity and the risk of

Table 2—*RR of type 2 diabetes according to physical activity from 1986 through 2002 (n = 68,907)*

MET hours of activity per week	<2.1	2.1–4.6	4.7–10.4	10.5–21.7	≥21.8	*P* for trend
n	1,010	784	769	796	671	
Person-years (1,034,808)	161,509	165,568	206,597	229,903	271,231	
Age-adjusted RR	2.66 (2.41–2.94)	2.10 (1.89–2.33)	1.57 (1.42–1.74)	1.43 (1.29–1.59)	1.00	<0.001
Multivariate RR*	2.37 (2.15–2.16)	1.92 (1.73–2.13)	1.48 (1.34–1.64)	1.40 (1.26–1.55)	1.00	<0.001
Multivariate RR including continuous BMI*	1.66 (1.50–1.83)	1.56 (1.41–1.74)	1.30 (1.17–1.44)	1.27 (1.15–1.41)	1.00	<0.001

Data are RR (95% CI). *Adjusted for age (5-year interval), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), alcohol consumption (0, 0.1–4.9, 5–14.9, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes.

type 2 diabetes. In the joint analyses, higher physical activity within each BMI category was associated with decreased risk of diabetes, whereas elevated BMI even in the highest category of physical activity markedly increased the risk for type 2 diabetes. Similarly, increased walking pace decreased the risk of diabetes within each weight category, although the risk was still 13-fold among obese brisk walkers versus normal-weight brisk walkers.

Physical activity is known to decrease the risk of type 2 diabetes (5,6). Although physical activity has multiple beneficial effects that can improve insulin and glucose delivery to muscle (21), it may not fully abolish the adverse effects of obesity (22). Obesity is known to increase peripheral insulin resistance and reduce β-cell sensitivity to glucose (23). Production of adipokines from adipocytes is known to influence insulin sensitivity and type 2 diabetes (24). The increased plasma concentration of inflammatory mediators, such as tumor necrosis factor-α and interleukin-6 induced by obesity (25), may interfere with insulin action by suppressing insulin signal transduction. Weight loss may therefore be a key mechanism to reduce the secretion of these factors by decreasing adipose tissue volume and subsequently reducing the risk of diabetes. Even moderate weight loss (5% of body weight) can improve insulin action, decrease fasting blood glucose concentrations, and reduce the need for diabetes medications (26–28).

The current study has some potential limitations. Some under-diagnosis of diabetes is likely because screening for blood glucose was not feasible, given the size of the cohort. Our participants are all health professionals and have ready access to care; over 98% of them reported fasting glucose screening in the past 4 years. Thus, undiagnosed diabetes should be relatively low in our cohort. However, we cannot exclude the possibility that obese people were more likely to be diagnosed than nonobese people. Moreover, under-ascertainment of cases, if not associated with exposure, would not be expected to affect the RR estimates (29).

We did not assess cardiorespiratory fitness. However, physical activity is the primary modifiable determinant of fitness, and even modest levels of physical activity (e.g., 30 min/day of brisk walking) can achieve levels of cardiorespiratory fitness that have been associated with a significant reduction in mortality risk (30). Our physical activity variable included only leisure time activity. Other activities such as household chores and occupational activities may also affect the risk for diabetes. Measurement errors in self-reported physical activity are inevitable, and nondifferential misclassification may have biased the association of physical activity with risk of type 2 diabetes toward the null. However, this should not substantially affect the analyses stratified according to physical activity levels. Our validation studies using physical activity diaries indicated good reproducibility and validity of self-reported physical activity. Our previous analysis showed that physical activity predicted the risk of diabetes (5) and other chronic diseases (18). Moreover, physical activity was assessed regularly during follow-up, and use of the repeated measures in the analyses not only dampened measurement errors but also took into account real changes in physical activity levels over time.

Our analyses of the combined effects of physical activity and obesity have direct public health implications. The adverse effects of body fatness on type 2 diabetes

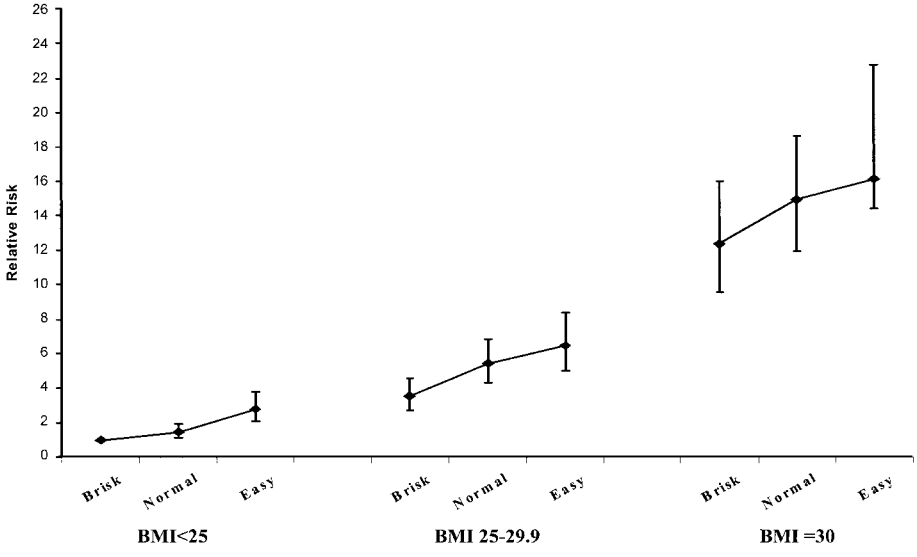

Figure 1—*RRs of type 2 diabetes according to usual walking pace among women who did not perform vigorous (<6 METs) activities and categories of BMI in the Nurses' Health Study 1986–2002. Data are adjusted for age (5-year interval), smoking status (never; past; or current smoker of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 1–4, 5–14, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes. Walking pace was specified as easy (<3.2 km/h), normal (3.2–4.8 km/h), brisk (4.8–6.2 km/h), and very brisk (≥6.4 km/h).*

Table 3—*Multivariate RRs of type 2 diabetes according to categories of BMI, waist circumference, and physical activity from the Nurses' Health Study from 1986 through 2002*

	MET hours of activity per week					
	<2.1	2.1–4.6	4.7–10.4	10.5–21.7	≥21.8	*P* for trend
BMI (kg/m^2)						
<25						
Multivariate-adjusted RR*	2.08 (1.66–2.61)	1.64 (1.29–2.08)	1.50 (1.20–1.88)	1.58 (1.28–1.96)	1 (Ref.)	<0.001
25–29.9						
Multivariate-adjusted RR*	6.87 (5.67–8.33)	6.30 (5.18–7.66)	5.10 (4.20–6.21)	5.35 (4.41–6.48)	4.76 (3.92–5.79)	<0.001
30						
Multivariate-adjusted RR*	16.75 (13.99–20.04)	15.76 (13.06–19.01)	13.01 (10.74–15.75)	12.93 (10.64–15.71)	10.74 (8.74–13.18)	<0.001
	MET hours of activity per week					
	Inactive (<2)		Moderate (2.0–5.9)		Vigorous (≥6)	
Waist circumference tertiles (inches)						
<28						
Multivariate-adjusted RR*	2.01 (1.08–3.73)		1.20 (0.58–2.49)		1 (Ref.)	
Multivariate RR further adjusted for continuous BMI*	2.16 (1.15–4.04)		0.99 (0.44–2.24)		1 (Ref.)	
29–31						
Multivariate-adjusted RR*	5.24 (3.52–7.82)		4.57 (3.08–6.79)		3.73 (2.62–5.32)	
Multivariate RR further adjusted for continuous BMI*	4.22 (2.79–6.36)		3.75 (2.50–5.64)		3.10 (2.15–4.46)	
≥32						
Multivariate-adjusted RR*	22.26 (15.75–31.45)		19.87 (14.04–28.11)		15.92 (11.34–22.35)	
Multivariate RR further adjusted for continuous BMI*	10.26 (7.14–14.74)		9.74 (6.78–13.98)		8.22 (5.77–11.71)	

Data are RR (95% CI). *Adjusted for age (5-year interval), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), alcohol consumption (0, 0.1–4.9, 5–14.9, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes.

risk were persistent in both lower and higher physical activity categories. Conversely, the benefits of physical activity were not limited to lean women; among those who were overweight and obese, physically active women tended to have lower type 2 diabetes risk than sedentary women. Our findings are in line with Finnish Diabetes Prevention Study (32) and the Diabetes Prevention Program study (33) that found that even modest weight loss led to substantial reduction in diabetes risk. Given the difference in the magnitude of risk contribution of adiposity versus physical activity to the development of type 2 diabetes, weight loss and maintenance of healthy weight should be emphasized as an eventual goal to prevent the onset of type 2 diabetes.

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