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Relationship of Physical Activity vs Body Mass Index With Type 2 Diabetes in Women

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Context Physical inactivity and body mass index (BMI) are established independent risk factors in the development of type 2 diabetes; however, their comparative importance and joint relationship with diabetes are unclear.

Objective To examine the relative contributions and joint association of physical activity and BMI with diabetes.

Design, Setting, and Participants Prospective cohort study of 37 878 women free of cardiovascular disease, cancer, and diabetes with 6.9 years of mean follow-up. Weight, height, and recreational activities were reported at study entry. Normal weight was defined as a BMI of less than 25; overweight, 25 to less than 30; and obese, 30 or higher. Active was defined as expending more than 1000 kcal on recreational activities per week.

Main Outcome Measure Incident type 2 diabetes, defined as a new self-reported diagnosis of diabetes.

Results During the follow-up, 1361 cases of incident diabetes occurred. Individually, BMI and physical activity were significant predictors of incident diabetes. Compared with normal-weight individuals, the multivariate-adjusted hazard ratio (HR) was 3.22 (95% confidence interval [CI], 2.69-3.87) for overweight individuals and 9.09 (95% CI, 7.62-10.8) for obese individuals. For overall activity (kilocalories expended per week), compared with the least active first quartile, the multivariate-adjusted HRs were 0.91 (95% CI, 0.79-1.06) for the second quartile, 0.86 (95% CI, 0.74-1.01) for the third, and 0.82 (95% CI, 0.70-0.97) for the fourth (P for trend=.01). In the combined analyses, overweight and obese participants, whether active or inactive, had significantly elevated risks, compared with normal-weight active individuals. The multivariate-adjusted HRs were 1.15 (95% CI, 0.83-1.59) for normal-weight inactive, 3.68 (95% CI, 2.63-5.15) for overweight active, 4.16 (95% CI, 3.05-5.66) for overweight inactive, 11.5 (95% CI, 8.34-15.9) for obese active, and 11.8 (95% CI, 8.75-16.0) for obese inactive participants.

Conclusions Although BMI and physical inactivity are independent predictors of incident diabetes, the magnitude of the association with BMI was greater than with physical activity in combined analyses. These findings underscore the critical importance of adiposity as a determinant of diabetes.

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P HYSICAL INACTIVITY AND BODY mass index (BMI) are established independent risk factors in the development of type 2 diabetes mellitus; however, the comparative importance and joint relationship of these factors on diabetes is unclear.[1-4] In the 1990s, the prevalence of both obesity and diabetes nearly doubled, demonstrating the significance of each as a major public health issue.[5]

Data on the interrelationship between BMI and physical activity and the risk of diabetes are limited. Some large clinical trials have investigated the effect of diet and exercise interventions on high-risk individuals; however, most did not distinguish between the effects of weight vs exercise, and all were performed on participants with impaired glucose tolerance.[6-8] There are few observational studies that directly evaluate the joint relationship between BMI and physical activity with diabetes in a population of healthy women.[9]

A clearer understanding of the combined effect of BMI and physical activity is needed to stratify patients by risk and in turn target those at highest risk of developing diabetes. Therefore, we investigated the combined relation-

ship of BMI and physical activity with diabetes to understand whether increasing physical activity levels reduce the elevated risk of diabetes from obesity. In addition, because walking is the most common form of exercise in women, we also considered walking in our analysis of physical activity.[10-12]

METHODS
Participants

Participants were from the Women's Health Study (WHS), an ongoing ran-

domized double-blinded clinical trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular

disease (CVD) and cancer. Beginning in 1992, 39 876 US female health care professionals aged 45 years and older, free of CVD, cerebrovascular disease, and cancer were recruited and randomized into the study.[13,14] Data were collected on sociodemographics, health habits, and medical history. For this study, 1998 women were excluded due to missing data on physical activity or BMI or because of a preexisting diagnosis of diabetes, which left 37 878 women as the baseline population. The protocols of the WHS, including obtaining informed consent, have been approved by the Brigham and Women's Hospital institutional review board.

Assessment of BMI, Physical Activity, and Other Covariates

Using self-reported height and weight from the baseline questionnaire, BMI was calculated by dividing weight in kilograms by height in meters squared.

Women were also asked to estimate the average time (0, 1-19 min/wk, 20-59 min/wk, 1 h/wk, 1.5 h/wk, 2-3 h/wk, 4-6 h/wk, or ≥7 h/wk) they spent on 8 groups of recreational activities during the past year: walking or hiking; jogging (>10-minute mile); running (≤10-minute mile); bicycling; aerobic exercise, aerobic dance, or the use of exercise machines; lap swimming; tennis, squash, or racquetball; and lower-intensity exercise (including yoga, stretching, and toning).[15] Additionally, the number of flights of stairs climbed daily (0, 1-2, 3-4, 5-9, 10-14, or ≥15) was assessed. A metabolic equivalent task (MET) score was assigned based on the energy cost of each activity. Since 1 MET is approximately 1 kcal/kg of body weight per hour, we were able to estimate energy expenditure in kilocalories per week by multiplying the MET score by body weight and hours per week (using the mid point of the time category). This measurement of physical activity has been shown to be valid and reliable. The test-retest correlation over 2 years in a random sample of nurses was 0.59. When questionnaire estimates were compared with 4 past-week physical ac-

tivity recalls collected the year before the questionnaire was administered, the correlation was 0.79 and when compared with activity diaries during the same year for 4 separate weeks, the correlation was 0.62.[16]

Participants also reported age (years), family history of diabetes in a first-degree relative (yes, no), alcohol use (rare, 1-3 drinks per month, 1-6 drinks per week, ≥1 drink per day), smoking status (never, past, current), use of hormone therapy (never, past, current), history of hypertension (yes, no), and history of high cholesterol (yes, no). Women completed semiquantitative food frequency questionnaires from which folate, saturated fat, vitamin E, fiber, and fruit and vegetable intake was calculated.[17] Hypertension was defined as self-reported high blood pressure diagnosed by a physician, a self-reported systolic blood pressure of 140 mm Hg or higher, or diastolic blood pressure of 90 mm Hg or higher. High cholesterol was defined as self-reported high cholesterol diagnosed by a physician, self-reported total cholesterol level of 240 mg/dL (≥6.6 mmol/L) or higher, or use of cholesterol-lowering medications.

Ascertainment of Diabetes Mellitus

Self-reported diabetes status was evaluated at baseline, and women with a history of diagnosed diabetes were excluded. Since participants were aged at least 45 years at baseline, incident diabetes mellitus was classified as type 2 diabetes. Thereafter, all of the participants provided annual self-reports whether and when they had been diagnosed with type 2 diabetes since completing their previous questionnaire.

Two complementary approaches have been used to confirm self-reported type 2 diabetes in the WHS. First, we attempted to contact 473 women with self-reported diabetes who provided a blood sample as part of a nested case-control study of diabetes to verify the self-reported diagnosis. Based on the American Diabetes Association (ADA) diagnostic criteria, diabetes cases were confirmed if 1 or more of the following

were present: (1) 1 or more symptom of hyperglycemia in conjunction with either a fasting plasma glucose level of at least 126 mg/dL or a random plasma glucose level of at least 200 mg/dL; (2) in the absence of symptoms, 2 or more elevated plasma glucose measurements (fasting plasma glucose of ≥126 mg/dL, random plasma glucose of ≥200 mg/dL, or plasma glucose of ≥200 mg/dL at ≥2 hours during oral glucose tolerance testing); (3) use of insulin or an oral hypoglycemic agent.[18] Using the ADA criteria, the self-reported diagnosis of diabetes was confirmed in 406 (91%) of 446 women who responded via telephone interview.[19] Second, a random sample of 147 women with self-reported diabetes was mailed a supplemental diabetes questionnaire, also using the ADA criteria to parallel the telephone interview. Among 136 respondents, 124 (91%) women were identified as having diabetes by the supplemental questionnaire. In addition, 113 of the 124 women gave permission to contact their primary care physician. Ninety-seven of the 113 physicians responded, of whom 90 provided adequate information to apply the ADA criteria. For these 90 women, 89 (99%) were confirmed to have type 2 diabetes. Thus, we believe that self-reported type 2 diabetes is valid in the WHS.

Statistical Analysis

All analyses were conducted using SAS statistical software version 8 (SAS Institute, Cary, NC). Based on the current World Health Organization guidelines, BMI was divided into 3 categories: normal weight, less than <25; overweight, 25 to less than 30; and obese, 30 or higher.[20] Mean (SDs) were calculated for all continuous variables and the percentage of participants in each category was determined for all categorical variables. Analyses of covariance were run for continuous variables and χ^2 tests for trend were run for categorical variables to determine if statistically significant differences were present.

Physical activity was categorized in 3 ways: (1) by categories of energy expenditure: inactive, fewer than 1000 kcal/wk

or active, more than 1000 kcal/wk since 1000 kcal/wk satisfies current recommendations for physical activity; ie, either 30 minutes of moderate-intense activity on 5 days of the week or 20 minutes of vigorous-intense activity on 3 days of the week[10,21]; (2) by quartiles of energy expenditure: fewer than 200, 200 to 599, 600 to 1499, and 1500 or more kcal/wk; and (3) by time spent walking per week (no walking, <1, 1-1.5, 2-3, and ≥4 h/wk). Cox proportional hazards models examined the independent effects of both BMI and physical activity on diabetes. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using age- and multi-

variate-adjusted models, which included the previously described covariates and randomized WHS treatments. Additional multivariate-adjusted models controlled for all previously mentioned covariates, plus total kilocalories per week in the BMI analysis and BMI in the physical activity analyses. To test for overall effect modification, we created an interaction term with the continuous BMI and physical activity (kilocalories per week) variables, which was included in both age- and multivariate-adjusted models that included the independent continuous variables.

To investigate the combined effect of BMI and physical activity on the devel-

opment of diabetes, joint BMI and physical activity variables were created. That is, participants were divided into groups based on both their BMI and physical activity level. Joint variables were created for each of the 3 different classifications of physical activity described previously with the 3-level BMI variable. For example, 6 groups of women were represented for the BMI and dichotomous physical activity combined analysis: normal-weight active, normal-weight inactive, overweight active, overweight inactive, obese active, and obese inactive. The normal-weight, most active individuals were always the referent group. Age- and multivariate-adjusted models were generated with the joint variables using Cox proportional hazards regression. Cox proportional hazards assumptions were tested using time-varying variables. Analyses of time spent walking also adjusted for total energy expenditure in kilocalories per week. To test for effect modification in each joint analysis, an interaction term was defined by multiplying the categorical physical activity variable and the 3-level BMI variable, which was individually entered into each age- and multivariate-adjusted Cox proportional hazards model to generate HRs and their 95% CIs.

RESULTS

Of the 37 878 women, 1361 developed type 2 diabetes during 6.9 mean years of follow-up. At baseline, 19 630 participants (52%) were normal weight, 11 700 (31%) were overweight, and 6548 (17%) were obese. The mean (SD) BMI was 25.9 (5.0). In all, 12 936 participants (34%) were considered active based on the current recommendations (≥1000 kcal/wk) and the median (interquartile range) energy expenditure was 581 (1148) kcal/wk.

The baseline characteristics of the participants by BMI category are shown in **TABLE 1**. Women who were overweight or obese were more likely to have a family history of diabetes, hypertension, and high cholesterol. Body mass index was inversely associated

Table 1. Characteristics of Women by Body Mass Index Category at Baseline*

| | Body Mass Index | | | |
Variable	<25 (n = 19 630)	25 to <30 (n = 11 700)	≥30 (n = 6548)	P Value
Body mass index, mean (SD)	22.3 (1.7)	27.2 (1.4)	34.4 (4.1)	<.001†
Physical activity, median (IQR), kcal/wk	650 (1163)	567 (1155)	393 (983)	<.001†
Age, mean (SD), y	54.5 (7.1)	55.0 (7.1)	53.8 (6.5)	<.001†
Years of follow-up, mean (SD)	7.0 (0.8)	6.9 (1.0)	6.6 (1.4)	<.001†
Person-years of follow-up	136 876	80 690	43 488	<.001†
Family history of diabetes, No. (%)	4166 (21.2)	3126 (26.7)	2121 (32.4)	<.001‡
Hormone therapy, No. (%)				
Never	9015 (46.0)	5531 (47.4)	3498 (53.5)	<.001‡
Past	1775 (9.1)	1260 (10.8)	792 (12.1)	
Current	8803 (44.9)	4889 (41.9)	2243 (34.3)	
Hypertension, No. (%)§	3144 (16.0)	3294 (28.2)	2910 (44.5)	<.001‡
High cholesterol level, No. (%)‖	4904 (25.0)	3827 (32.7)	2163 (33.1)	<.001‡
Smoking status, No. (%)				
Never	9895 (50.4)	5986 (51.2)	3463 (53.0)	<.001‡
Past	6934 (35.4)	4284 (36.7)	2347 (35.9)	
Current	2787 (14.2)	1417 (12.1)	730 (11.2)	
Alcohol use, No. (%)				
Rare	7525 (38.3)	5422 (46.4)	3788 (57.9)	<.001‡
1-3 drinks/mo	2557 (13.0)	1584 (13.5)	864 (13.2)	
1-6 drinks/wk	6944 (35.4)	3652 (31.2)	1580 (24.1)	
≥1 drink/d	2599 (13.2)	1039 (8.9)	314 (4.8)	
Intake, mean (SD) Fruits and vegetables, servings/d	6.2 (3.6)	6.1 (3.5)	6.0 (3.9)	.01†
Fiber, g/d	19.4 (6.2)	18.9 (5.7)	18.0 (5.4)	<.001†
Folate, µg/d	442 (230)	424 (221)	396 (210)	<.001†
Saturated fat, g/d	19.1 (4.9)	19.8 (4.7)	21.0 (4.8)	<.001†
Vitamin E, mg/d	6.8 (5.1)	6.6 (5.0)	6.2 (3.5)	<.001†

Abbreviation: IQR, interquartile range.
*Percentages may not sum to 100 due to rounding.
†P Value, analysis of variance.
‡P Value, χ² test of trend.
§Hypertension was defined as self-reported high blood pressure diagnosed by a physician, a self-reported systolic blood pressure of at least 140 mm Hg, or diastolic blood pressure of at least 90 mm Hg.
‖High cholesterol was defined as self-reported high cholesterol diagnosed by a physician, self-reported total cholesterol of at least 240 mg/dL (6.6 mmol/L), or use of cholesterol-lowering medications.

with energy expenditure per week, hormone therapy use, smoking status, and regular alcohol consumption.

The independent effects of BMI and physical activity on diabetes in both age and multivariate-adjusted models are presented in TABLE 2, TABLE 3, TABLE 4, and TABLE 5. Overweight participants had an increased risk of diabetes with a multivariate HR of 3.22, and obese participants had an even greater HR of 9.09 (Table 2).

Those who met the physical activity guidelines had a lower risk of incident diabetes with an age-adjusted HR of 0.73 (Table 3). Although adjustment for confounders attenuated the association with physical activity, the relationship remained significant. Additional adjustment for BMI further attenuated the HR. Further analysis of physical activity as energy expenditure in quartiles and time spent walking (Table 3) revealed a reduction in the HR of diabetes as activity increased. There was no significant overall effect modification of physical activity (kilocalorie per week) by BMI when the interaction between the continuous BMI and physical activity variables was analyzed ($P = .46$).

Examination of the combined effect of BMI and physical activity is shown in TABLE 6. With the exception of the normal-weight inactive group, each group had a statistically significant increased risk of diabetes compared with the normal-weight active reference group. When the inactive group and active group within the same BMI strata were compared, the HR decreased from 4.16 to 3.68 ($P = .28$) for overweight participants and from 11.8 to 11.5 ($P = .73$) for obese participants. These decreases in risk were small and nonsignificant. However, within the same activity level, when the overweight and obese groups were compared with the normal-weight group, there were large increases in the HRs ($P < .01$). Tests of proportional hazards revealed changes over time in physical activity and in the obese-active and obese-inactive groups. However, taking into account updated information on BMI at 24, 36, and

72 months and updated information on physical activity at 36 and 72 months, the HRs did not change appreciably. Although hypertension and high cholesterol may be correlated with diabetes, multivariate models that individually excluded these covariates did not alter the interpretation of the results.

Further analysis of the joint effect of BMI and physical activity, as energy expenditure per week in quartiles, in the multivariate model is displayed in FIGURE 1. As before, as physical activity level increased, there was a small reduction in the relative risk of incident diabetes within each BMI group. However, as BMI increased the magnitude of the HRs increased dramatically. For example, in obese participants, the HR decreased from 14.6 for the least active to 14.0 for the most active quartile ($P = .68$). In contrast, when comparing those in the highest physical activity quartile, the obese group's risk of diabetes was 14-fold that of the normal weight group ($P < .01$). The rela-

Table 2. Hazard Ratios of Diabetes Mellitus by Body Mass Index

	Body Mass Index Category			
Variable	Normal Weight (n = 19 630)	Overweight (n = 11 700)	Obese (n = 6548)	P for Trend
No. (%) of women with diabetes mellitus	178 (0.9)	421 (3.6)	762 (11.6)	
Hazard ratio (95% CI)				
Age adjusted	1.00	3.99 (3.35-4.76)	14.0 (11.9-16.4)	<.001
Multivariate adjusted*	1.00	3.22 (2.69-3.87)	9.09 (7.62-10.8)	<.001
Multivariate adjusted†	1.00	3.22 (2.69-3.87)	9.06 (7.60-10.8)	<.001

Abbreviation: CI, confidence interval.
*Adjusted for age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups.
†Adjusted for aforementioned covariates and physical activity.

Table 3. Hazard Ratios of Diabetes Mellitus by Physical Activity Category

Variable	Inactive*	Active†
Women, No. (%)		
Total	24 942 (65.8)	12 936 (34.2)
With diabetes mellitus	985 (3.9)	376 (2.9)
Adjusted hazard ratio (95% CI)		
Age	1.00	0.73 (0.65-0.83)
Multivariate‡	1.00	0.85 (0.75-0.97)
Multivariate§	1.00	0.91 (0.80-1.03)

Abbreviation: CI, confidence interval.
*Energy expenditure was less than 1000 kcal/wk.
†Energy expenditure was at least 1000 kcal/wk.
‡Adjusted for age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups.
§Adjusted for aforementioned covariates and body mass index.

Table 4. Hazard Ratios of Diabetes Mellitus by Expediture of Energy

	Energy Expenditure, kcal/wk				
Variable	0-199	200-599	600-1499	≥1500	P for Trend
Women, No. (%)					
Total	9735 (25.7)	9541 (25.2)	10 517 (27.8)	8085 (21.3)	
With diabetes mellitus	478 (4.9)	337 (3.5)	306 (2.9)	240 (3.0)	
Adjusted hazard ratio (95% CI)					
Age	1.00	0.72 (0.62-0.82)	0.58 (0.50-0.67)	0.60 (0.52-0.70)	<.001
Multivariate*	1.00	0.78 (0.68-0.90)	0.69 (0.59-0.80)	0.74 (0.63-0.88)	<.001
Multivariate†	1.00	0.91 (0.79-1.06)	0.86 (0.74-1.01)	0.82 (0.70-0.97)	.01

Abbreviation: CI, confidence interval.
*Adjusted for age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups.
†Adjusted for aforementioned covariates and body mass index.

tion between energy expenditure and diabetes risk was not influenced by BMI level ($P>.05$).

Next, the relationship of BMI and time spent walking on diabetes is shown in **FIGURE 2**. Body mass index continued to have a greater influence on the development of incident diabetes than physical activity in these analyses. When we considered the 1877 women who walked at least 7 hours per week, results were identical to women who walked at least 4 hours per week. The relation between time spent walking and risk of diabetes was not influenced by BMI level ($P>.05$). The combination of BMI and intensity level was also examined and demonstrated similar results as the models described previously.

COMMENT

Consistent with previous studies, we demonstrated that BMI and physical inactivity are significant predictors of type 2 diabetes.[1-4] This study further re-

vealed that the magnitude of the association with BMI is much greater than with physical activity, when examining the combined relationship of BMI and physical activity. We observed a modest reduction in the risk of diabetes with increasing physical activity level compared with a large increase in the risk with increasing BMI. In this study, joint analyses broaden our understanding of risk factors' relative influence on diabetes.

These findings parallel the limited data on the combined effects of physical activity and BMI. In one observational analysis examining multiple risk factors for diabetes, being overweight or obese was also found to be the strongest predictor in women in the Nurses' Health Study.[9]

Our results are also consistent with several randomized clinical trials in diabetes prevention among participants with impaired glucose tolerance. The Diabetes Prevention Program found that lifestyle modification, including physi-

cal activity, diet modification, and weight loss, was more beneficial than metformin therapy in reducing the development of diabetes.[6] The Da Qing Impaired Glucose Tolerance and Diabetes Study compared diet and exercise interventions and found similar reductions in the risk of diabetes while controlling for BMI.[7] In both studies, the precise contribution of weight and physical activity is unclear. Tuomilehto et al[8] found that improvement in diet and exercise reduced the risk of diabetes even when participants did not attain their targeted weight loss; however, this study did not examine the effect of exercise on diabetes risk based on BMI category.[8] Each of these studies involved high-risk individuals, whereas our cohort included apparently healthy women free of baseline diabetes.

Blumenthal et al,[22] in their trial of participants with hypertension, found that weight loss had a significantly greater effect on the reduction of fasting glucose and insulin levels than

Table 5. Hazard Ratios of Diabetes Mellitus by Physical Activity*

	Time Spent Walking, h/wk†					P for Trend
Variable	None	<1	1 to 1.5	2 to 3	≥4	
Women, No. (%)						
Total	76 661 (21.6)	10 002 (26.4)	8171 (21.6)	6373 (16.8)	5620 (14.9)	
With diabetes mellitus	418 (5.1)	386 (3.9)	250 (3.1)	146 (2.3)	161 (2.9)	
Adjusted hazard ratio (95% CI)						
Age	1.00	0.72 (0.63-0.83)	0.56 (0.48-0.65)	0.41 (0.34-0.50)	0.51 (0.42-0.61)	<.001
Multivariate‡	1.00	0.82 (0.71-0.95)	0.68 (0.58-0.80)	0.49 (0.40-0.60)	0.64 (0.53-0.78)	<.001
Multivariate§	1.00	0.95 (0.82-1.10)	0.87 (0.73-1.02)	0.66 (0.54-0.81)	0.89 (0.73-1.09)	.004

Abbreviation: CI, confidence interval.
*Analyses were limited to the 37 828 women who provided complete information on time spent walking.
†Additionally adjusted for kilocalorie per week expended on activities other than walking in multivariate models.
‡Adjusted for age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups.
§Adjusted for aforementioned covariates and body mass index.

Table 6. Hazard Ratios of Diabetes Mellitus by Both Body Mass Index and Physical Activity

	Normal Weight		Overweight		Obese	
Variable	Active†	Inactive‡	Active†	Inactive‡	Active†	Inactive‡
Women, No. (%)						
Total	7223 (19.1)	12 407 (32.8)	3943 (10.4)	7757 (20.5)	1770 (4.7)	4778 (12.6)
With diabetes mellitus	56 (0.8)	122 (1.0)	125 (3.2)	296 (3.8)	195 (11.0)	567 (11.9)
Adjusted hazard ratio (95% CI)						
Age	1.00	1.25 (0.91-1.72)	4.61 (3.32-6.40)	5.44 (4.02-7.34)	17.5 (12.9-23.9)	18.6 (13.9-24.8)
Multivariate*	1.00	1.15 (0.83-1.59)	3.68 (2.63-5.15)	4.16 (3.05-5.66)	11.5 (8.34-15.9)	11.8 (8.75-16.0)

Abbreviation: CI, confidence interval.
*Adjusted for body mass index, age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups.
†Energy expenditure at least 1000 kcal/wk.
‡Energy expenditure less than 1000 kcal/wk.

physical activity. Elevated glucose and insulin levels are precursors to the development of diabetes. Thus, if glucose and insulin levels decrease, the rate of diabetes may also decrease, consistent with our results.

Why does physical activity appear to have a stronger effect overall than when explored by BMI strata? Although BMI and physical inactivity are viewed as 2 independent variables, they may be influencing each other and contributing to the same causal pathway leading to the development of diabetes. This is suggested by the attenuation of the effects of physical activity by adjusting for BMI in our analyses.
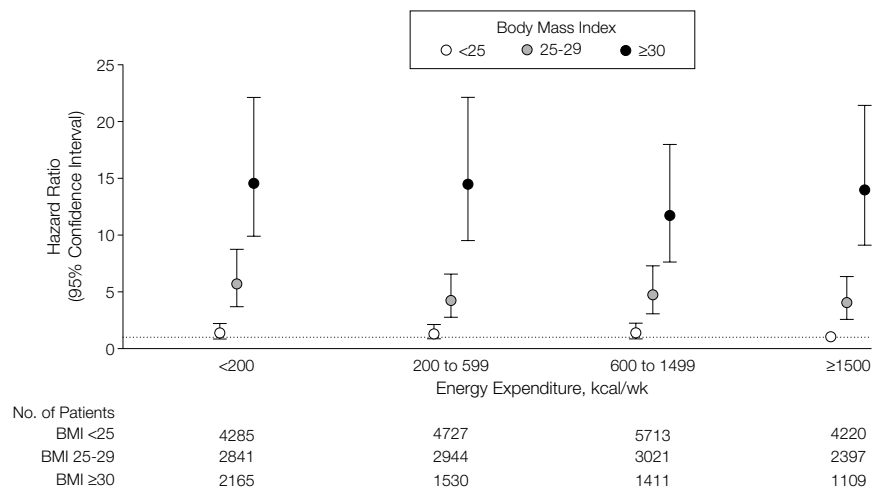
Although there are many theories, the mechanism by which obesity affects insulin resistance and in turn leads to diabetes remains poorly understood. Obesity is known to increase peripheral insulin resistance and reduces beta cell sensitivity to glucose.[23,24] Although physical activity increases insulin sensitivity and has complex effects that can improve glucose metabolism, such as insulin-receptor upregulation in muscle and increased insulin and glucose delivery to muscle, it may not fully reverse the effects of obesity.[25] It has also been postulated that adipose tissue affects insulin metabolism by releasing free fatty acids and cytokines.[23,26] 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.

Limitations of our study include the use of self-reported diabetes. However, a validation study comparing self-reports with additional medical information resulted in confirmation of at least 91% of the self-reported cases, consistent with findings from the Nurses' Health Study.[4] Since diabetes is self-reported, we may be missing cases that are not yet diagnosed. If anything, this would result in an underestimate of the true effect. The physical activity variables may also be subject to measurement error. However, studies have shown that the self-reported physical activity questionnaire used in this study is both valid and reliable.[16] Only rec-

reational, and not occupational activity, was reported, but all women are health care professionals who tend to perform little occupational physical ac-

tivity. Even though activity may be somewhat underestimated, we do not expect this to bias our findings. Although the women in this cohort tend
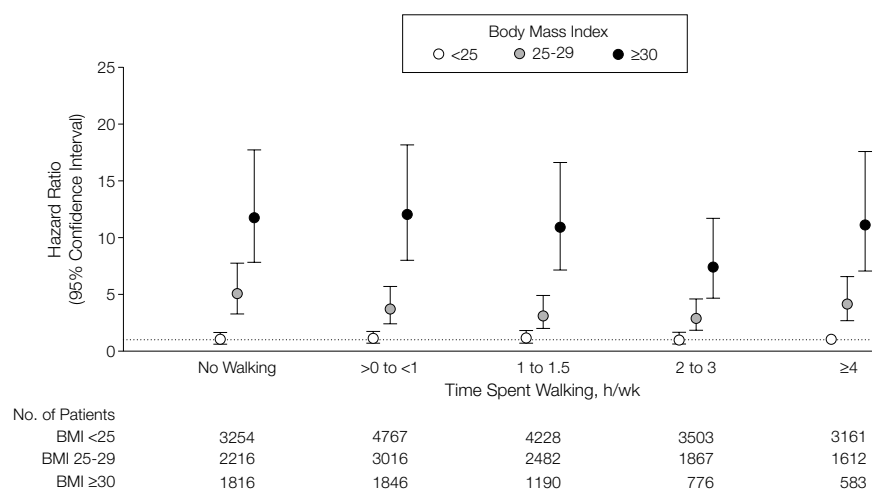
Figure 1. Joint Relation of Body Mass Index vs Physical Activity in Quartiles With the Hazard Ratio of Incident Diabetes

No. of Patients	<200	200 to 599	600 to 1499	≥1500
BMI <25	4285	4727	5713	4220
BMI 25-29	2841	2944	3021	2397
BMI ≥30	2165	1530	1411	1109

Error bars indicate 95% confidence interval. The referent group includes women with a body mass index lower than 25 and whose energy expenditure exceeded 1500 kcal/wk.

Adjusted for body mass index, age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups. Analyses were limited to the 36 363 women who provided complete information on physical activity, body mass index, and all covariates described above.

Figure 2. Joint Relation of Body Mass Index vs Time Spent Walking With the Hazard Ratio of Incident Diabetes

No. of Patients	No Walking	>0 to <1	1 to 1.5	2 to 3	≥4
BMI <25	3254	4767	4228	3503	3161
BMI 25-29	2216	3016	2482	1867	1612
BMI ≥30	1816	1846	1190	776	583

Error bars indicate 95% confidence interval. The referent group includes women with a body mass index lower than 25 and who walked at least 4 h/wk.

Adjusted for body mass index, age, family history of diabetes, alcohol use, smoking status, hormone therapy use, hypertension, high cholesterol, dietary factors, and randomized Women's Health Study treatment groups. Analyses were limited to the 36 317 women who provided complete information on time spent walking, body mass index, and all covariates described above.

to be healthier than the general population,[27] the biological mechanisms that affect the development of diabetes are unlikely to be different compared with the general population. Future studies should incorporate the role of race or ethnicity, which we were underpowered to study. Finally, residual confounding by variables such as carbohydrate intake and baseline impaired fasting glucose level is always an issue in an observational study; however, major confounders have been controlled for in our multivariate models.

In conclusion, this study demonstrates that both physical activity and BMI play important roles in the development of type 2 diabetes. As opposed to our original hypothesis, physical activity only modestly affected the influence of BMI on diabetes risk, and rather the combination of risk factors attenuated the individual influence of physical activity. The magnitude of the association with diabetes risk was much greater for BMI than for physical activity. These findings underscore the critical importance of adiposity as a determinant of type 2 diabetes. Because physical activity is a significant individual predictor and has a beneficial effect on BMI, it remains an important intervention for diabetes prevention. Our study suggests that to further reduce the risk of diabetes with physical activity, it should be performed in conjunction with achieving weight loss. By furthering our understanding of the relative influence of BMI and activity on diabetes, we may improve our ability to risk stratify patients and in turn may reduce the incidence of diabetes.

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