Published in final edited form as:

Am J Med. 2009 December ; 122(12): 1115–1121. doi:10.1016/j.amjmed.2009.02.008.

Physical activity, body mass index and diabetes risk in men: A prospective study

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Abstract

Purpose—Physical activity has been associated with lower diabetes risk, but several prospective studies among women found that activity only slightly attenuated the diabetes risk associated with high BMI. We investigated the independent and joint associations between vigorous activity and BMI on diabetes risk in men.

Methods—This was a prospective cohort design within the Physicians' Health Study, using Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident diabetes in 20,757 men without diabetes at baseline. Models were based on self-reported BMI and exercise frequency at baseline, first separately and then with a 6-category joint variable combining World Health Organization BMI category (normal/overweight/obese) with activity status (active/inactive) using weekly vigorous activity as the threshold.

Results—After a median follow-up of 23.1 years, there were 1,836 cases of incident diabetes. Compared with active participants with normal BMIs, active but overweight and obese men had multivariable-adjusted HRs of 2.39 (95% CI, 2.11–2.71) and 6.22 (95% CI, 5.12–7.56). Inactive men with normal, overweight or obese BMIs had multivariable-adjusted HRs of 1.41 (95% CI, 1.19–1.67), 3.14 (95% CI, 2.73–3.62) and 6.57 (95% CI, 5.25–8.21).

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Author Contributions: Dr. Siegel had access to all data and takes responsibility for data integrity and analytical accuracy. Data analysis, interpretation: Siegel, Sesso, Bowman, Lee, Manson, Gaziano. Manuscript: Siegel. Critical revision: Sesso, Bowman, Lee, Manson, Gaziano. The corresponding author and co-authors have no conflicts of interest to disclose.

Conclusions—Active men with normal and overweight BMIs had lower diabetes hazards than their inactive counterparts, but no difference by weekly activity was seen in obese men. Elevated BMI is a key driver of diabetes risk, with relatively modest attenuation by activity.

Keywords

Diabetes; physical activity; body mass index; obesity

Type 2 diabetes is increasingly prevalent in the United States (US), with an estimated lifetime risk of 32.8% for men and 38.5% for women.¹ The 2007 figures from the National Center for Health Statistics showed that 25.6% of US adults were obese based on World Health Organization criteria ($\text{BMI} \geq 30 \text{ kg/m}^2$), and only 31% of all adults were sufficiently active to meet national recommendations for physical activity.² While activity decreases the risk of diabetes,^{3–5} and overweight and obesity increase that risk,^{6–8} less is known about the interrelationship between activity and body mass index (BMI), particularly among men.⁹

Previous analyses of BMI and activity controlled for BMI as a confounder of the association with diabetes risk.^{3,5,10} There is now a growing awareness of the importance of analyzing joint effects of BMI and activity as related to measures of health status and mortality.^{11,12} In a prospective study among initially healthy women, a joint analysis of physical activity and BMI revealed that activity did not significantly decrease risk in any BMI category¹¹ despite prior evidence showing a benefit when activity was studied separately.⁴

Therefore, our objective was to examine individual and joint associations among activity and BMI with the risk of type 2 diabetes in 20,757 middle-aged and older men followed for a median of 23.1 years.

Research Design and Methods

Study population

The Physicians' Health Study (PHS) was a randomized, controlled trial of aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer. Details on PHS study design and recruitment have been reported previously.¹³ The original cohort of 22,071 U.S. male physicians aged 40 to 84 years at enrollment has been followed continuously since 1982 via annual questionnaires, with approval from the Institutional Review Board at the Brigham and Women's Hospital (Boston, MA). The baseline questionnaire in 1982 covered demographic, lifestyle, and clinical factors. We excluded 647 participants with diabetes at baseline and an additional 291 men with below-normal BMI ($< 18.5 \text{ kg/m}^2$) or missing baseline data on height, weight, or exercise. We further excluded participants with missing data on potential confounders ($n=376$). Because a large proportion (12%) of participants was missing data on history of high cholesterol, we used an indicator variable for these men. In total, 20,757 men were followed for development of incident diabetes through March 1, 2006.

Ascertainment of BMI, physical activity, and other covariates

Baseline self-reported height in inches and weight in pounds were converted to height in meters (m) and weight in kilograms (kg); BMI was calculated as kg/m^2 . Self-reported height ($r=0.98$), weight ($r=0.95$), and BMI (0.96) have shown high correlations with measured values in a physician population.¹⁴ World Health Organization categories for BMI were used: normal weight (18.5 to $< 25 \text{ kg/m}^2$), overweight (25 to $< 30 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$).¹⁵ Duration of overweight or obesity was not available.

For physical activity, the baseline questionnaire in 1982 asked, "how often do you exercise vigorously enough to work up a sweat?" with six possible answer options ranging from "rarely/"

never” to “daily.” Following convention in prior PHS analyses and other exercise studies validated for distinguishing between active and inactive individuals,^{16, 17} we considered participants reporting vigorous exercise at least weekly to be “active.” Alcohol use and smoking were both measured by self report. Alcohol use was a 4-category frequency variable ($\geq$ once per day, often but not daily, 1–3 times per month, and rarely to never). Smoking was analyzed as a 3-category variable (current, past, never).

We used this dichotomous physical activity variable (active/inactive) for the main analysis, also combining the two most frequent exercise categories of “daily” and “5–6 times per week” on the basis of small numbers and similar physiology. We used the 5-category frequency of vigorous exercise as a secondary exposure variable and for an analysis using a more active cutpoint, at least 2–4 times weekly, closer to current guidelines calling for vigorous activity at least three times weekly.¹⁸ Other covariates included smoking, alcohol use, history of high cholesterol and hypertension.

Ascertainment of incident diabetes

Participants who self-reported diabetes at baseline, as diagnosed by their physicians, were excluded. During the study period, new diagnoses of diabetes mellitus to the month and year were obtained from self-report on questionnaires at 6 months and annually thereafter, corresponding to date of physician visit at diagnosis. Glucose testing was not available. Prior morbidity follow-up in this population has been found to be 99.7% complete.¹⁹ A validation study of self-reported diagnoses of type 2 diabetes among female health professionals found a positive predictive value of 91%.^{20, 21} Study participants were initially aged 40–84 years; new diagnoses were therefore presumed to be type 2 diabetes.²²

Statistical analyses

Baseline characteristics of the 20,757 participants were analyzed by WHO BMI category, using ANOVA to compare continuous variables and χ^2 for categorical variables. Cox proportional hazards models were used to calculate hazard ratios of incident type 2 diabetes for BMI category, activity, and the joint variable combining these parameters. The proportional hazards assumption was tested graphically and statistically using the logarithm of follow-up time and was satisfied for our primary analysis ($p=0.45$). Participants who died from any cause were censored on that date; those who did not develop diabetes before the end of follow-up were also censored.

For the first analysis, overweight and obese men were compared with the normal-BMI reference group regarding diabetes risk. We first adjusted for age and then added smoking, alcohol, high cholesterol and hypertension. Information on family history of diabetes and diet was not collected as part of the PHS. We added the 5-category exercise frequency variable to the model to study the independent association of BMI with diabetes risk.

To assess activity, we modeled the association of weekly vigorous exercise using inactive men as the reference. In a secondary analysis, we evaluated diabetes hazards by the activity variable, again with the least active group as the reference, and then stratified by BMI. Testing for a significant trend for BMI or physical activity was performed with an ordinal variable that included the median values for each category of BMI or activity frequency.

Finally, we examined the joint association of BMI and physical activity with the hazards of developing diabetes using the lean, active group as the reference. The three-category BMI and the two-category activity variables at baseline were used to create a joint variable that divided participants into six categories: 1) normal BMI/active; 2) normal BMI/inactive; 3) overweight/active; 4) overweight/inactive; 5) obese/active; and 6) obese/inactive.

Using Cox proportional hazards models, we calculated the hazard ratios of diabetes, first adjusting for age, and then adding lifestyle factors and health history, and finally adjusting for continuous BMI. We tested for effect modification in combined analyses by creating a multiplicative interaction term between BMI and activity categories and entering this term into each model to test for statistical significance. All analyses were conducted using SAS version 9.2 (Cary, NC). All p-values were two-sided with a significance level of $\alpha = 0.05$.

Results

After a median follow-up of 23.1 years (431,126 person-years) among initially non-diabetic men with an average baseline age of 53 years, there were 1,836 new cases of diabetes occurring in 8.9% of the population, with incidence rates for men in the normal, overweight and obese groups of 2.4, 6.1 and 15.0 cases per 1,000 person-years respectively. Men who reported vigorous activity at least weekly had a diabetes incidence rate of 3.7 per 1,000 person-years, compared with 5.8 per 1,000 in those who did not. The diabetes incidence rates for each category of increasing physical activity were 6.5, 5.1, 4.7, 3.7, and 2.8 per 1,000 person-years for the groups rarely or never active, active 1–3 times per month, $\geq$ once weekly, 2–4 times weekly, and ≥ 5 times weekly, respectively.

Baseline characteristics by combined BMI/activity category are shown in Table 1. In all BMI categories, the most commonly reported exercise frequency was 2–4 times per week, with once weekly next most common. Heavier men were less physically active overall, $p < 0.001$ for all comparisons. The normal BMI category had the lowest proportion reporting vigorous exercise rarely or never, at 11.7%, compared with 14.5% and 18.9% in the overweight and obese groups, respectively. The normal BMI category contained the highest proportion of active participants.

The hazards for diabetes in multivariable-adjusted models for elevated BMI were 2.38 (2.15–2.63) and 5.74 (4.93–6.69) for overweight and obese participants, respectively (data not shown). Adjustment for the five-category physical activity variable only modestly attenuated the hazard ratios.

Overall, physically active participants had an age-adjusted HR of 0.65 (0.59–0.72) (Table 2) compared with those who were inactive. After full adjustment, active men had a 20% reduced risk of developing diabetes compared with inactive men. Both hazard ratios changed by less than 5% using a more stringent cutpoint of vigorous exercise 2–4 times weekly. There was no significant effect modification of dichotomized activity by BMI in the fully-adjusted model ($p = 0.18$). When the fully-adjusted models were stratified by BMI, the HRs associated with activity for the normal, overweight, and obese groups were 0.74 (0.62–0.87); 0.76 (0.67–0.87); and 0.88 (0.68–1.14), respectively.

There was an inverse relationship between exercise frequency and diabetes risk Table 3 (p , interaction between 5-category exercise frequency and 3-category BMI = 0.02). In the BMI-stratified analysis, there was little difference between the two least active groups in all BMI categories, although the normal BMI category showed significant reduction. However, the inverse relationship strengthened with increasing frequency of activity, and the overweight and obese categories showed the most greatly reduced hazards; among obese participants, only the most active group ($n=77$) showed significant hazard reduction, 0.48 (0.25–0.91).

The joint association of BMI and physical activity on the risk of diabetes is shown in Table 4. Hazard ratios for incident diabetes increased with increasing BMI. Every cross-classified group had significantly increased risk of diabetes as compared with the normal weight-active group after full adjustment, with larger increases in hazards between BMI categories than between activity groups within BMI categories.

Within the normal and overweight categories, there were significant differences in hazard ratios by activity, with multivariable-adjusted relative hazards of 1.36 (95% CI: 1.15–1.61) and 1.31 (95% CI: 1.15–1.49), respectively, indicating significantly increased hazards from inactivity. In contrast, for obese participants, the association of weekly activity with diabetes risk was not significant, with a relative hazard of 1.13 (0.87–1.47).

We conducted a secondary analysis with the “active” cutpoint changed from weekly to 2–4 times weekly. The relationship remained constant, with significant differences in hazards between active/inactive groups within the normal and overweight BMI categories ($p < 0.001$, $p = 0.03$, respectively). In the obese category, however, the p -value was 0.08, which raises the possibility of a trend across categories. With a cutpoint at ≥ 5 times weekly, the difference between active and inactive groups in both the overweight and obese categories ($n = 1009$, $n = 77$ respectively) became statistically significant ($p = 0.01$). The difference between active and inactive at a normal BMI was not significant ($p = 0.17$).

Conclusions

In this prospective cohort study of 20,757 men, weekly vigorous activity reduced the hazards of type 2 diabetes for those who were normal weight or overweight when studied as a combined exposure. While regular activity showed the strongest overall association in obese men when studied as an isolated exposure, the joint analysis of regular activity and BMI together revealed that in the setting of elevated BMI, vigorous physical activity does not attenuate the harm of excess body weight to a significant degree until the frequency reaches ≥ 5 times weekly.

Studies in both men and women have found that the magnitude of diabetes-related risk for elevated BMI was greater than that for physical inactivity.^{7,11,23} When analyzing BMI and activity jointly, we found that diabetes risk was most strongly related to increasing BMI and comparatively less influenced by activity. While measures of each exposure differ in our study, preventing direct comparison, our findings are consistent with this prior research. Even among active participants, increasing BMI was strongly associated with increased diabetes risk, regardless of activity frequency cutpoint. There was significant risk attenuation among active subgroups of the normal and overweight BMI categories, but not in the obese category until activity frequency reached ≥ 5 times weekly, attained by only 9.2% of the obese population.

Our data underscore the importance of focusing on the combined relationships among physical activity, BMI and diabetes. This long-term prospective study in men adds a nuance to prior findings in women,¹¹ differing modestly from several studies that incorporated multiple measures of adiposity and more detailed measures of physical activity.^{8, 23} In the Women’s Health Study, no significant differences were found between active and inactive participants when BMI and physical activity were analyzed jointly in any BMI category. We may have seen a slightly stronger relationship because our study considered vigorous exercise rather than moderate, since higher-intensity exercise is associated with greater reduction in the risk of diabetes⁴ and other vascular endpoints.²⁴

Several biological mechanisms may partially explain why regular physical activity does not more strongly counteract the diabetes risk that has been associated with high BMI in observational studies. Type 2 diabetes is a multifactorial illness, and physical activity, along with cardiorespiratory fitness, can affect several points in this pathway, including enhanced insulin sensitivity, improved lipid metabolism, and decreased blood pressure.²⁵ Exercise-induced insulin sensitivity wanes after 24 hours,^{25,26} and the overall environment of disordered free fatty acid metabolism and inflammatory mechanisms involved in the pathogenesis of adiposity²⁷ may overpower the effects of activity. Excess weight is most likely a marker of extensive metabolic abnormalities that infrequent activity alone cannot counteract. However,

these competing effects argue for studying the effects of both measures of adiposity and of activity together rather than adjusting for one to study the other. The similar diabetes hazard reduction from very frequent exercise seen in all BMI categories (Table 3) adds valuable long-term observational data to that from trials involving a higher “dose” of exercise.²⁸

Self-reported physical activity, only a rough proxy for cardiorespiratory fitness, is a limitation of our study, since there is only moderate correlation between frequency of vigorous exercise and more detailed ascertainment of fitness among healthy adults ($r=0.57$).¹⁷ The limited detail on activity creates possible misclassification bias, as the relative imprecision of this variable as compared with BMI may differentially impact our ability to detect an association with physical activity. However, we would expect this to bias our results toward the null. Moreover, self-reported activity assessment has been validated in similar studies of health professionals^{5,11,23} and produces a conservative yet valid estimate of exercise effects. Self-reported activity data can differ by weight status, but good correlation with accelerometer data has been found in normal weight and overweight men.²⁹ We stratified by BMI to address this issue and restricted our main analysis to distinguishing between active and inactive populations given the limitations of the “sweat frequency” question.¹⁶ Moderate walkers may still be misclassified as inactive, but this would also bias our results toward the null. We did not update BMI or physical activity during follow-up to avoid reverse causation; however, studies that did so found either no significant change in risk¹¹ or a stronger protective effect of activity.⁵ The homogeneity of the PHS cohort by gender, race and socioeconomic status limits generalizability but minimizes potential confounding. The use of self-reported diabetes also leads to a conservative estimate, and undiagnosed cases may have different risk factors. Finally, there may be residual confounding by unmeasured lifestyle factors.

In this prospective cohort study of middle-aged and older men, high body mass index was a strong risk factor for incident diabetes. The risk from elevated BMI was modestly but significantly attenuated by weekly physical activity in normal weight and overweight men but was not significantly reduced in obese men until the frequency of vigorous activity reached ≥ 5 times weekly. These data are clinically useful as further evidence in men that the diabetes risk associated with a high BMI can be moderately attenuated by vigorous activity, but that the most protective clinical feature is a normal BMI.

Acknowledgments

We are indebted to the thousands of participants of the Physicians’ Health Study for their outstanding commitment and to the entire PHS staff for their expertise and assistance.

Funding/Support: The PHS is supported by grants CA-34944 and CA-40360 and CA-097193 from the National Cancer Institute and grants HL-26490 and HL-34595 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Dr. Siegel received support from the Office of Research and Development, Cooperative Studies Program, Department of Veterans Affairs.

Role of the Sponsors: The sponsors had no role in study design or conduct; collection, management, analysis, or interpretation of data; or preparation, review, or finalization of the manuscript.

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Table 1

Baseline characteristics of participants by BMI/physical activity classification, with active defined as $\geq$ once/week.

Variable	18.5 to <25 kg/m ²		25 to <30 kg/m ²		$\geq$ 30 kg/m ²	
N=20,757	Active	Inactive	Active	Inactive	Active	Inactive
N, % of overall population	9,075 (43.7)	2,928 (14.1)	5,507 (26.5)	2,407 (11.6)	520 (2.5)	320 (1.5)
Cases of diabetes (N, %)	414 (4.6)	197 (6.7)	623 (11.3)	363 (15.1)	140 (26.9)	99 (30.9)
Age, mean (SD), years	52.4 (9.6)	53.9 (9.8)	53.2 (9.0)	53.6 (9.0)	52.2 (8.6)	53.2 (9.0)
BMI, mean (SD)	23.0 (1.3)	23.0 (1.3)	26.6 (1.3)	26.8 (1.4)	32.3 (2.4)	32.8 (3.3)
History of hypertension, (treated or > 140), %	17.8	20.5	27.7	29.5	39.2	42.8
History of high cholesterol (treated or > 240), %	9.4	10.8	11.5	11.1	11.4	9.7
Daily alcohol use, %	26.2	25.5	24.4	23.5	19.0	18.4
Current smoking, %	8.9	13.9	10.6	14.5	13.7	14.1
Exercise frequency, N						
1 ($\geq$ 5x/wk)	2,317	-	1,009	-	77	-
2 (2-4x/wk)	4,683	-	2,911	-	260	-
3 (1x/wk)	2,075	-	1,587	-	183	-
4 (1-3/mo)	-	1,526	-	1,256	-	161
5 (rarely/never)	-	1,402	-	1,151	-	159

P<0.001 for the χ^2 statistics for all categorical variables and for the ANOVA tests comparing means for continuous variables.

Table 2Hazard ratios of incident diabetes by dichotomized activity, with active defined as $\geq$ once/week.

	Inactive	Active
N (%)	5,655 (27.2)	15,102 (72.8)
N (cases)	659	1,177
Total person-years	114,579	316,547
Age	1.00	0.65 (0.59, 0.72)
Multivariate [†]	1.00	0.70 (0.64, 0.77)
Multivariate [‡]	1.00	0.77 (0.70, 0.85)
Multivariate[†], stratified by BMI		
Normal BMI (n=12,003, total person-years=252,465)	1.00	0.74 (0.62, 0.87)
N (cases)	197	414
Person-years	60,135	192,331
Overweight (n=7,914, total py= 162,701)	1.00	0.76 (0.67, 0.87)
N (cases)	363	623
Person-years	48,425	114,276
Obese (n=840, total py=15,960)	1.00	0.88 (0.68, 1.14)
N (cases)	99	140
Person-years	6,019	9,940

[†] Adjusted for age, smoking, alcohol use, history of high cholesterol, and history of hypertension.[‡] Additionally adjusted for World Health Organization BMI group.

p, interaction = 0.18 for dichotomized activity and BMI group in the fully-adjusted model.

Table 3

Hazard ratios of incident diabetes by 5-category activity category.

	Rarely/never	1-3/month	Once/week	2-4x/week	≥5 times/wk	p, trend
N (%)	2,712 (13.1)	2,943 (14.2)	3,845 (18.5)	7,854 (37.8)	3,403 (16.4)	
N (cases)	343	316	375	606	196	
Person-years	52,867	61,712	79,898	165,641	71,008	
Age	1.00	0.79 (0.68, 0.93)	0.74 (0.64, 0.86)	0.57 (0.50, 0.65)	0.43 (0.36, 0.52)	<0.001
Multivariate [†]	1.00	0.84 (0.72, 0.98)	0.78 (0.68, 0.91)	0.63 (0.55, 0.73)	0.49 (0.41, 0.59)	<0.001
Multivariate [‡]	1.00	0.84 (0.72, 0.98)	0.81 (0.70, 0.93)	0.69 (0.61, 0.79)	0.58 (0.48, 0.69)	<0.001
Multivariate[†], stratified by BMI						
Normal BMI	1.00	0.75 (0.56, 0.99)	0.84 (0.65, 1.08)	0.57 (0.45, 0.73)	0.59 (0.45, 0.78)	<0.001
N (cases)	111	86	127	193	94	
Person-years	27,726	32,409	43,762	99,758	48,810	
Overweight	1.00	0.83 (0.68, 1.02)	0.72 (0.59, 0.88)	0.72 (0.61, 0.87)	0.57 (0.44, 0.73)	<0.001
N (cases)	187	176	190	343	90	
Person-years	22,269	26,156	32,681	60,944	20,651	
Obese	1.00	1.13 (0.76, 1.69)	1.17 (0.78, 1.74)	0.96 (0.66, 1.40)	0.48 (0.25, 0.91)	0.08
N (cases)	45	54	58	70	12	
Person-years	2,872	3,147	3,454	4,939	1,547	

[†] Adjusted for age, alcohol use, smoking status, history of high cholesterol, and history of hypertension.

[‡] Additionally adjusted for WHO BMI group. All p <0.05.

P, interaction = 0.02 for BMI group and 5-category activity variable.

Table 4

Hazard ratios of incident diabetes by joint variable, comparing all groups to normal BMI/active as reference.

	18.5 to < 25 kg/m ²		25 to <30 kg/m ²		>30 kg/m ²	
	Active	Inactive	Active	Inactive	Active	Inactive
N, %	9,075 (75.6)	2,928 (24.4)	5,507 (69.6)	2,407 (30.4)	520 (61.9)	320 (38.1)
N (cases)	414	197	623	363	140	99
Person-years	192,331	60,135	114,276	48,425	9,940	6,019
Age	1.00	1.49 (1.26, 1.76)	2.62 (2.31, 2.96)	3.60 (3.13, 4.15)	7.87 (6.50, 9.54)	8.85 (7.11, 11.02)
Multivariate [†]	1.00	1.41 (1.19, 1.67)	2.39 (2.11, 2.71)	3.14 (2.73, 3.62)	6.22 (5.12, 7.56)	6.57 (5.25, 8.21)

[†] Adjusted for age, alcohol use, and smoking status, history of high cholesterol and history of hypertension.

* Relative hazard and 95% CI between active and inactive members within normal BMI category: 1.36 (1.15, 1.61). For overweight category, relative HR: 1.31 (1.15, 1.49). For obese category, 1.13 (0.87, 1.47), p=0.34.

P, trend <0.001. All p<0.001 for comparisons to the reference group; other comparisons as shown.