The Joint Effects of Physical Activity and Body Mass Index on Coronary Heart Disease Risk in Women

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Background: Physical activity and body mass index (calculated as weight in kilograms divided by height in meters squared) independently alter the risk of coronary heart disease (CHD); however, their combined effect on CHD is not established. Our objective was to study the combined association of physical activity and body mass index on CHD.

Methods: Prospective cohort study of 38,987 women free of cardiovascular disease, cancer, and diabetes at baseline in the Women’s Health Study, with 10.9 mean years of follow-up. Weight, height, and recreational activities were reported on entry. Body mass index was categorized as normal weight (<25), overweight (25 to <30), and obese (≥30). Active was defined as 1000 kilocalories or more expended on recreational activities weekly. Six joint body weight-physical activity categories were defined. The main outcome measure was the occurrence of incident CHD during follow-up, defined as a cardiovascular event including nonfatal myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or CHD death.

Results: A total of 948 cases of incident CHD occurred during follow-up. Higher body mass index and physical inactivity were individual predictors of CHD. In joint analyses, compared with active normal-weight individuals, the multivariate-adjusted hazard ratios (95% confidence intervals) were 1.54 (1.14-2.08) for overweight-active; 1.87 (1.29-2.71) for obese-active; 1.08 (0.84-1.39) for normal weight-inactive; 1.88 (1.46-2.42) for overweight-inactive; and 2.53 (1.94-3.30) for obese-inactive. Increasing levels of walking also resulted in significant reductions in CHD risk for overweight and obese individuals.

Conclusions: The risk of CHD associated with elevated body mass index is considerably reduced by increased physical activity levels. However, the risk is not completely eliminated, reinforcing the importance of being lean and physically active.

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PARTICIPANTS

The Women’s Health Study (WHS) is a recently completed, randomized, double-blind, clinical trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease (CVD) and cancer. A total of 39,876 US female health professionals 45 years or older, reportedly free of CHD, CVD, and cancer, were enrolled and randomized beginning in 1992. Data were collected on sociodemographics, health habits, and medical history. For the
present study, 889 participants were excluded because of missing data on physical activity or BMI or a history of myocardial infarction (MI), coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or stroke, leaving 38,987 baseline subjects.

**ASSESSMENT OF BMI AND PHYSICAL ACTIVITY**

Body mass index was calculated with baseline self-reported height and weight. In the Nurses' Health Study, a similar cohort, recalled weight had a correlation of 0.96 with directly measured weight and recalled height had a correlation of 0.94, demonstrating high validity. Women were asked to estimate the average time per week spent during the past year on the following 8 groups of recreational activities: walking and hiking; jogging; running; bicycling; aerobic exercise, aerobic dance and exercise; swimming; tennis, squash, and racquetball; and lower-intensity exercise. The number of flights of stairs climbed daily was also reported. Based on the energy cost of each activity, a metabolic equivalent task (MET) score was assigned. One MET is approximately 1 kcal/kg of body weight per hour; thus, energy expenditure in kilocalories per week was estimated by multiplying the MET score by body weight and hours per week. This assessment 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. Questionnaire estimates compared with 4 past-week physical activity recalls collected the year before the questionnaire was administered had a correlation of 0.79. Questionnaire estimates compared with activity diaries during the same year for 4 separate weeks had a correlation of 0.62.

**ASCERTAINMENT OF CHD DURING FOLLOW-UP**

After the first 6 and 12 months and annually thereafter, subjects completed follow-up questionnaires that assessed their compliance in taking assigned treatment, potential adverse effects and adherence in taking data on physical activity or BMI or a history of myocardial infarction (MI), coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or stroke, leaving 38,987 baseline subjects.

Subjects were divided into a 6-group joint physical activity and BMI variable: normal weight-active, normal weight-inactive, overweight-active, overweight-inactive, obese-active, and obese-inactive. We also considered other definitions of total physical activity (in quartiles: <200, 200-599, 600-1499, and ≥1500 kcal/wk); and walking (time spent per week: no walking, <1, 1-1.5, 2-3, and ≥4 h/wk).

Cox proportional hazards models examined the independent association of both BMI and physical activity with CHD. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using age + treatment– and multivariate-adjusted models. The primary multivariate model adjusted for age, parental history of MI before age 60 years (yes or no), alcohol use (rarely/never, 1-3 drinks/week, 4-6 drinks/week, or ≥7 drinks/week), smoking status (never, past, or current), hormone therapy use (never, past, or current), dietary factors (saturated fat, fiber, vitamin E, folate, and fruit and vegetable intake) calculated from a semiquantitative food frequency questionnaire, and randomized WHS treatments. Information on these variables was obtained by self-report at baseline. Though randomized active and placebo treatment assignments were evenly distributed across the groups, we controlled for randomized treatment to ensure that it had no influence on the results.

In secondary analyses, we controlled for the aforementioned covariates plus self-reported hypertension, high cholesterol level, and diabetes, which are likely intermediates in the causal pathway to the development of CHD and may reflect overadjustment. Hypertension was defined as self-reported high blood pressure, diagnosed by a physician, self-reported systolic blood pressure of 140 mm Hg or higher, or diastolic blood pressure of 90 mm Hg or higher. In a small unpublished validation study in the WHS, the confirmation rate was 96% for self-reported hypertension. In another study, greater than 90% of WHS participants reporting no hypertension throughout follow-up were confirmed to be normotensive. High cholesterol level was defined as self-reported high cholesterol level diagnosed by a physician, self-reported total cholesterol of 240 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0259), or use of cholesterol-lowering medications. In a recent study of the WHS, the Pearson and Spearman correlation coefficients were 0.54 and 0.57 (P <.001) for self-reported and measured total cholesterol, respectively. Self-reported high cholesterol level was a strong predictor of CVD. In validation studies using telephone interviews or supplemental questionnaires, the positive predictive value of diabetes was very high in the WHS (91%).

Walking analyses adjusted for kilocalories per week on activities other than walking. Categorical variables containing each subgroup were entered into each model to calculate the test of trend. To test for overall effect modification, we tested an interaction term between the continuous BMI and physical activity (kilocalories per week) variables in both age + treatment– and multivariate-adjusted models.

Joint BMI and physical activity variables were entered into age + treatment– and multivariate-adjusted models to study their combined association with incident CHD. The normal-weight (BMI <25), most active (≥1000 kcal/wk) individuals were always considered the reference group. The assumption of proportional hazards was tested for each model and was not violated. To control for residual confounding due to body weight, interaction terms between BMI and the difference from the mean BMI for each strata were entered into each model. In secondary analyses, we limited analyses to the hard CHD end points, nonfatal and fatal MI. To test for effect modification in each joint analysis, an interaction term between BMI and each physical activity variable was entered into each model. P <.05 was considered statistically significant.
RESULTS

Of the 38,987 women at baseline, 948 developed CHD during 10.9 mean years of follow-up. At baseline, 34% of the women were considered physically active based on the Surgeon General’s guidelines. Median energy expenditure was 378 kcal/wk, and mean (SD) BMI was 26.0 (5.1). Of the women, 51% were considered normal weight; 31%, overweight; and 18%, obese. The Spearman correlation between MET score and kilocalories per week was 0.99 (P < .001).

Baseline characteristics of the subjects by the 6-category joint physical activity and BMI variable are given in Table 1. Elevated BMI was associated with hypertension, high cholesterol level, and diabetes and inversely associated with hormone therapy use, physical activity, and alcohol use. Inactive women were more likely to be current smokers.

In Table 2, as BMI increased, the risk of CHD increased even after adjusting for potential confounders (P < .001 for trend), with an HR of 1.64 for overweight women and 2.13 for obese women. Subjects who were physically active, as defined by the Surgeon General guidelines,7,9 had a 31% reduction in risk with an age + treatment–adjusted HR of 0.69. When potential confounders were added, the HR was attenuated but remained significant (HR, 0.82; 95% CI, 0.70–0.96). For total physical activity and walking, there was a significant reduction in CHD risk even after adjusting for potential confounders. In additional analyses, we controlled for BMI in the physical activity models and for physical activity in the BMI models. Small changes in the HRs were found that did not alter the interpretation of the results.

There was no significant overall effect modification of physical activity (kilocalories per week) by BMI (P = .61); thus, BMI and physical activity remained independent predictors. No effect modification of physical activity by BMI status was found (P = .31–.84) in each joint model.

The joint effect of BMI and physical activity on CHD is shown in Figure 1. Compared with the normal weight–active group, CHD risk increased in overweight and obese subjects regardless of physical activity status in the multivariate model. As BMI increased in inactive women, there was an increase in the risk of CHD between each group (P value for normal weight–inactive vs overweight–inactive, < .001; P value for overweight–inactive vs obese–inactive, < .005). Among active women, there was a statistically significant difference between normal-weight women and overweight or obese women (P value for overweight–active vs normal weight–active, .005; P value for obese–active vs normal weight–active, .001); however, there was no statistically significant difference between overweight and obese groups (P = .32).

Similarly, when physical activity was delineated into quartiles of overall energy expenditure and jointly analyzed with BMI on CHD risk, increasing physical activity reduced the risk of CHD (Figure 2). As physical activity level increased, the difference in the risk of CHD between BMI strata decreased. Compared with normal-weight women, the HR remained significantly elevated (P < .01) in overweight and obese women irrespective of physical activity level, except for the overweight women who expended more than 1500 kcal/wk. Within each physical activity strata we found significant trends for increasing BMI (P values ranging from < .001 to .01). Within each BMI strata, trends were not significant for increasing physical activity level (P values ranging from .06 to .60).

In Table 3, increases in walking time reduced the risk of CHD, as did lower BMI levels. Similar to previous analyses, the risk of CHD decreased in each BMI strata as time spent walking increased. The greatest reduction in risk for each weight category occurred between no walking and 1.0
to 1.5 hours of walking per week. Among the overweight and obese, physical activity significantly reduced the risk of CHD; however, HRs remained elevated.

Adjustment for hypertension, high cholesterol level, and diabetes in each model considerably attenuated the risk of CHD; however, the trends across categories remained similar. The risk was reduced by approximately 16% in overweight women and by approximately 35% in obese women. When we excluded subjects with baseline and incident diabetes from our study population, the overall trends remained intact, but the magnitudes of the HRs were weakened. During the course of the study, 353 additional subjects developed MI. The overweight and obese active (≥1500 kcal/wk) had a 0.57 (0.47-0.69) reduction in risk compared to the reference group. The risk was reduced by approximately 20% to 40%. Therefore, these 3 intermediate factors accounted for a moderate amount of attenuation of the overall associations of elevated BMI and physical inactivity with CHD and likely explain a modest attenuation of the overall associations of elevated BMI and physical inactivity with CHD; however, the trends across categories remained similar.

In an earlier subgroup analysis of the WHS, physical activity attenuated the risk of CHD from elevated BMI (≥25). However, even high levels of physical activity did not eliminate the excess risk of CHD associated with overweight and obesity. Although there was no significant interaction between physical activity and BMI, this study improves our understanding of their interrelationship in the development of CHD. Limited data are available on the combined relationship of physical activity and BMI, typically assessed as subgroup analyses within studies that were not specifically designed to comprehensively assess the joint effect. When the interrelationship of BMI and physical activity with CHD was evaluated, we found that physical activity attenuated the risk of CHD from elevated BMI (≥25). However, even high levels of physical activity did not eliminate the excess risk of CHD associated with overweight and obesity. Although there was no significant interaction between physical activity and BMI, this study improves our understanding of their interrelationship in the development of CHD.

In this population of middle-aged and older women, both elevated BMI and reduced physical activity individually increased the risk of CHD, as in previous studies. When the interrelationship of BMI and physical activity with CHD was evaluated, we found that physical activity attenuated the risk of CHD from elevated BMI (≥25). However, even high levels of physical activity did not eliminate the excess risk of CHD associated with overweight and obesity. Although there was no significant interaction between physical activity and BMI, this study improves our understanding of their interrelationship in the development of CHD.

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tion with CVD risk; however, obesity was attenuated by risk factors, suggesting that obesity is a modifiable coronary risk factor. However, overweight individuals were not differentiated from normal-weight individuals, and the self-reported physical activity data were not as detailed. In this study, physical activity were defined as low (almost or completely inactive), moderate (some activity/week) or high (vigorous activity/week).

The Women’s Ischemia Syndrome Evaluation study, which analyzed the joint relationship of physical fitness and BMI with CVD risk, suggested that obesity is a modifiable risk factor by physical fitness. Follow-up extended only 4 years, and only symptomatic individuals were evaluated; therefore, the effect on a healthy population is unclear. Although physical fitness has been used as a proxy for physical activity, it likely reflects a nonmodifiable genetic component, which may influence other protective pathways. Physical activity measures are more practical because they are modifiable, simpler to quantify, and easier to understand by the public, and they can be directly used to formulate public health guidelines. The Nurses’ Health Study recently showed that obesity conferred greater risk than physical activity in joint analyses of BMI and physical activity on CHD risk. We were able to study high levels of physical activity that could not be evaluated in the Nurses’ Health Study.

Our results can be explained by the current understanding of the pathophysiologic processes of CHD. Adipocytes release free fatty acids, interleukins, and cytokines that may have adverse effects on cardiac function by accelerating atherosclerosis and increasing endothelial dysfunction, coagulability, and inflammation. There is evidence that physical activity improves endothelial function and reduces vascular resistance. Physical activity also reduces fibrinogen and platelet aggregation and increases tissue plasminogen activator levels, which likely reduces the risk of thrombosis. The mechanism by which physical activity attenuates the negative effect of obesity on CHD remains unclear. We postulate that the beneficial effect of physical activity may directly reduce and combat the ill effect of the prothrombotic factors released by adipocytes.
In conclusion, both physical activity and BMI play an important role in the development of CHD. We observed that the risk associated with BMI in CHD is reduced considerably by physical activity. This suggests that regular physical activity reduces the risk of CHD in women and that further coronary benefits will accrue from maintaining a healthy weight. Our study strongly supports current physical activity guidelines recommending 30 minutes of moderate activity daily to reduce chronic disease. This level of activity improved CHD risk regardless of baseline BMI. Furthermore, this study suggests that more than 30 minutes of physical activity daily further reduces the risk. Even high quantities of physical activity are unlikely to fully reverse the risk of CHD in overweight and obese women without concurrent weight loss. Regardless of body weight, these data highlight the importance of counseling all women to participate in increasing amounts of regular physical activity and maintaining a healthy weight to reduce the risk of CHD.

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Author Contributions: Dr Weinstein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Weinstein, Sesso, Lee, Manson, and Gaziano. Acquisition of data: Lee, Buring, and Gaziano. Analysis and interpretation of data: Weinstein, Sesso, Lee, Rexrode, Cook, Manson, and Gaziano. Drafting of the manuscript: Weinstein. Critical revision of the manuscript for important intellectual content: Weinstein.
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