WALKING COMPARED WITH VIGOROUS EXERCISE FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN

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Abstract

Background The role of walking, as compared with vigorous exercise, in the prevention of cardiovascular disease remains controversial. Data for women who are members of minority racial or ethnic groups are particularly sparse.

Methods We prospectively examined the total physical-activity score, walking, vigorous exercise, and hours spent sitting as predictors of the incidence of coronary events and total cardiovascular events among 73,743 postmenopausal women 50 to 79 years of age in the Women's Health Initiative Observational Study. At base line, participants were free of diagnosed cardiovascular disease and cancer, and all participants completed detailed questionnaires about physical activity. We documented 345 newly diagnosed cases of coronary heart disease and 1551 total cardiovascular events.

Results An increasing physical-activity score had a strong, graded, inverse association with the risk of both coronary events and total cardiovascular events. There were similar findings among white women and black women. Women in increasing quintiles of energy expenditure measured in metabolic equivalents (the MET score) had age-adjusted relative risks of coronary events of 1.00, 0.73, 0.69, 0.68, and 0.47, respectively (P for trend, <0.001). In multivariate analyses, the inverse gradient between the total MET score and the risk of cardiovascular events remained strong (adjusted relative risks for increasing quintiles, 1.00, 0.89, 0.81, 0.78, and 0.72, respectively; P for trend <0.001). Walking and vigorous exercise were associated with similar risk reductions, and the results did not vary substantially according to race, age, or body-mass index. A brisker walking pace and fewer hours spent sitting daily also predicted lower risk.

Conclusions These prospective data indicate that both walking and vigorous exercise are associated with substantial reductions in the incidence of cardiovascular events among postmenopausal women, irrespective of race or ethnic group, age, and body-mass index. Prolonged sitting predicts increased cardiovascular risk. (N Engl J Med 2002;347:716-25.)

PHYSICAL activity has been associated with a reduced risk of cardiovascular disease in epidemiologic studies,[1,2] but data for women and members of minority ethnic groups have been sparse. Moreover, the specific role of walking, the most common form of exercise among women,[3] has been addressed only minimally. Federal guidelines from the Centers for Disease Control and Prevention and the American College of Sports Medicine,[4] as well as the Surgeon General's Report on Physical Activity and Health,[3] endorse at least 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week, in contrast to earlier guidelines that recommended vigorous endurance exercise for at least 20 minutes three or more times per week.[5] Although the federal guidelines encourage a level of activity that is safe, accessible, and feasible for most Americans[6] (at least 75 percent of whom have less than the recommended level of activity[3]), the potential benefits of moderate-intensity activity in preventing cardiovascular events remain uncertain. Moreover, the role of time spent in sedentary behavior, such as sitting, in predicting risk remains relatively unexplored.

We therefore compared the roles of walking and vigorous exercise in the prevention of coronary and cardiovascular events in a large, ethnically diverse cohort of postmenopausal women. Using detailed assessments of physical activity, we examined the magnitude of associations between each of the measures of physical activity (the total physical-activity score, the intensity of exercise [walking vs. vigorous exercise], and the hours spent sitting) and the incidence of cardiovascular events.

METHODS

Study Population

The study population consisted of 73,743 women who were enrolled in the Women's Health Initiative Observational Study, which

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involved a national, multicenter cohort of postmenopausal women who were 50 to 79 years of age at entry. The Women's Health Initiative is a prospective, ethnically and racially diverse, multicenter clinical trial and observational study designed to address the major causes of illness and death in postmenopausal women (see the Appendix for a list of study investigators). A total of 93,676 women were enrolled in the observational study at 40 clinical centers between 1994 and 1998. Criteria for exclusion from the study included the presence of any medical condition associated with predicted survival of less than three years (e.g., class IV congestive heart failure, obstructive lung disease requiring supplemental oxygen, or severe chronic liver or kidney disease), alcoholism, mental illness, or dementia. In addition, women were excluded from the present analyses if, at base line, they had a history of coronary heart disease, stroke, or cancer; were nonambulatory (unable to walk at least one block); or had missing data on the physical-activity questionnaire. After women had been excluded for these reasons, 73,743 women remained in the analysis. Of these women, 61,574 were non-Hispanic white, 5661 were non-Hispanic black, 2880 were Hispanic, 2288 were Asian or Pacific Islander, and 1340 were American Indian or of other racial or ethnic background. Race was self-assigned. Details of the scientific rationale, design, eligibility requirements, and base-line characteristics of the cohort have been published elsewhere.[7]

Exposure Assessment

All women enrolled in the Observational Study were required to come for a clinic visit for base-line screening. At this visit, women completed self-administered questionnaires related to personal and family medical history, physical activity, smoking, diet, and other behavioral and lifestyle-related factors. Clinical measurements including height, weight, waist and hip circumferences, and blood pressure were obtained by trained staff members. All women provided written informed consent, and the study protocol was approved by the institutional review board of each center.

Recreational physical activity was assessed by a detailed questionnaire on the frequency and duration of walking and of several other types of activity (strenuous, moderate, and mild). Walking was assessed by a series of questions about the frequency of walks outside the home for more than 10 minutes without stopping, the average duration of each walk, and the usual walking pace. Vigorous exercise was defined as that in which "you work up a sweat and your heart beats fast," and examples included aerobics, aerobic dancing, jogging, tennis, and swimming laps. Moderate exercise was defined as that which was "not exhausting," and examples included biking outdoors, using an exercise machine (such as a stationary bicycle or a treadmill), calisthenics, easy swimming, and popular or folk dancing. Examples of mild exercise were slow dancing, bowling, and golf. Using a standardized classification of the energy expenditure associated with physical activities,[8] we calculated a weekly energy-expenditure score in metabolic equivalents (MET score) for walking and for total physical activity. Finally, participants were asked to estimate the number of hours per day they spent engaged in sedentary behavior, including time spent sitting as well as lying down or sleeping.

Reproducibility and Validation of the Physical-Activity Assessment

A sample of participants in the Observational Study (1092 women) was recruited into a reliability study to assess the reproducibility of selected questionnaires, including the physical-activity assessment. The average time between base line and repeated assessments was three months. The test–retest reliability for recreational physical activity, including walking and strenuous activity, was assessed (weighted kappas among all women ranged from 0.67 to 0.71).[7] The intraclass correlation coefficient for the primary summary variable (total energy expenditure in MET from all recreational physical activity) was 0.77. A similar physical-activity questionnaire has been found to be correlated with physical-activity diaries ($r=0.62$) and with one-week recall of activity ($r=0.79$) in a cohort of female health professionals.[9]

Ascertainment of End Points

The primary end points for this study were newly diagnosed coronary heart disease (nonfatal myocardial infarction or death from coronary causes) and total cardiovascular events (myocardial infarction, death from coronary causes, coronary revascularization, angina, congestive heart failure, stroke, or carotid revascularization) that occurred after the return of the base-line questionnaire but before August 27, 2000. Newly diagnosed cardiovascular events were identified on the basis of annual mailed follow-up questionnaires (response rates have been above 95 percent), and permission to review medical records was requested. Study physicians with no knowledge of the self-reported risk-factor status reviewed the records. The diagnosis of nonfatal myocardial infarction was confirmed if data in the hospital record met standardized criteria of diagnostic electrocardiographic changes, elevated cardiac-enzyme levels, or both.[10] Treatment with coronary or carotid revascularization was confirmed by documentation of the procedure in the medical record. The presence of angina was confirmed by hospitalization and confirmatory evidence on angiography, diagnostic stress test, or diagnosis by a physician and medical treatment. The occurrence of stroke was confirmed by documentation in the medical record of the rapid onset of a neurologic deficit consistent with stroke and lasting at least 24 hours or until death. The presence of congestive heart failure was confirmed by hospitalization and diagnostic confirmatory tests.

Fatal coronary disease was considered confirmed if there was documentation in the hospital or autopsy records or if coronary disease was listed as the cause of death on the death certificate and evidence of previous coronary disease was available. For deaths from other cardiovascular causes, a review of confirmatory evidence by physician-adjudicators was required.

Statistical Analysis

Our primary analyses used the detailed physical-activity assessment at base line. Person-time for each woman was calculated from the date of return of the base-line questionnaire to the date of a confirmed cardiovascular event, death from any cause, or August 27, 2000, whichever came first. Age-adjusted relative risks were computed as the incidence rate in a specific category of activity divided by the incidence rate in the lowest quintile, with adjustment for one-year age categories. We conducted tests of linear trend by treating the categories as a continuous variable and assigning the median score for each category.[11] All tests of statistical significance were two-sided.

We used Cox proportional-hazards regression[12] to adjust simultaneously for potential confounding variables, including age, smoking status, body-mass index (the weight in kilograms divided by the square of the height in meters), the ratio of the waist circumference to the hip circumference, alcohol consumption, age at menopause, use of hormone-replacement therapy, parental history of premature myocardial infarction (before 55 years of age in the father or before 65 years of age in the mother), race or ethnic group, education, family income, and several dietary variables. Additional models controlled for history or absence of history of hypertension, diabetes, and high cholesterol levels, as well as for functional status and a summary score for mental and emotional health.[13] The total MET score, the MET score for walking, time spent in vigorous exercise, walking pace, and hours spent sitting and lying down or sleeping were analyzed separately. Differences in the results for activity according to race (white women vs. black women), age, and body-mass index were assessed. Secondary analyses excluded data for the first year of follow-up in order to minimize potential bias caused by the presence of subclinical disease.

RESULTS

During up to 5.9 years of follow-up (mean, 3.2 years; total, 232,971 person-years), we documented 345 newly diagnosed cases of coronary disease (287 nonfatal myocardial infarctions and 58 deaths from coronary causes), 309 strokes, and 1551 first cardiovascular events among the 73,743 women 50 to 79 years of age who completed a detailed physical-activity questionnaire, were ambulatory, and were free of cardiovascular disease and cancer at base line. The base-line characteristics of the cohort and the distribution of physical-activity profiles and other risk factors have been described elsewhere.[7]

The total physical-activity score (in MET-hours per week) at base line had a strong inverse relation with the risk of coronary heart disease during the follow-up period (Table 1). In age-adjusted analyses, the relative risk declined with increasing quintiles of the total MET score (1.00, 0.73, 0.69, 0.68, and 0.47, respectively; P for trend <0.001). Risk reductions for increasing categories of walking (P for trend = 0.004) were similar to those for increasing categories of vig-

TABLE 1. RELATIVE RISKS OF CARDIOVASCULAR DISEASE ACCORDING TO QUINTILE OF TOTAL PHYSICAL-ACTIVITY SCORE AND CATEGORIES OF WALKING AND VIGOROUS EXERCISE.*

CATEGORY	QUINTILE OF TOTAL MET-HR PER WK					P VALUE FOR TREND
	1 (LOWEST)	2	3	4	5 (HIGHEST)	
Total exercise						
Total MET score (MET-hr/wk)						
Median	0	4.2	10.0	17.5	32.8	
Range	0–2.4	2.5–7.2	7.3–13.4	13.5–23.3	≥23.4	
Coronary heart disease						
No. of cases	92	70	68	70	45	
No. of person-years	44,989	45,329	46,003	49,338	47,312	
Age-adjusted relative risk (95% CI)	1.00	0.73 (0.53–0.99)	0.69 (0.51–0.95)	0.68 (0.50–0.93)	0.47 (0.33–0.67)	<0.001
Total cardiovascular disease						
No. of cases	396	342	304	281	228	
No. of person-years	44,448	44,836	45,550	48,948	46,972	
Age-adjusted relative risk (95% CI)	1.00	0.83 (0.71–0.95)	0.72 (0.62–0.84)	0.63 (0.54–0.74)	0.55 (0.47–0.65)	<0.001
Multivariate relative risk (95% CI)	1.00	0.89 (0.75–1.04)	0.81 (0.68–0.97)	0.78 (0.66–0.93)	0.72 (0.59–0.87)	<0.001
Walking						
Energy expenditure (MET-hr/wk)						
Median	0	1.5	3.8	7.5	16.7	
Range	None	0.1–2.5	2.6–5.0	5.1–10.0	>10.0	
Coronary heart disease						
No. of cases	133	64	52	47	49	
Age-adjusted relative risk (95% CI)	1.00	0.71 (0.53–0.96)	0.60 (0.44–0.83)	0.54 (0.39–0.76)	0.61 (0.44–0.84)	0.004
Total cardiovascular disease						
No. of cases	550	322	249	236	194	
Age-adjusted relative risk (95% CI)	1.00	0.88 (0.77–1.01)	0.70 (0.60–0.81)	0.66 (0.57–0.77)	0.58 (0.49–0.68)	<0.001
Multivariate relative risk (95% CI)	1.00	0.91 (0.78–1.07)	0.82 (0.69–0.97)	0.75 (0.63–0.89)	0.68 (0.56–0.82)	<0.001
Vigorous exercise						
Energy expenditure (min of strenuous exercise/wk)						
Median	0	30	90	140	210	
Range	None	1–60	61–100	101–150	>150	
Coronary heart disease						
No. of cases	269	35	13	14	14	
Age-adjusted relative risk (95% CI)	1.00	1.12 (0.79–1.60)	0.56 (0.32–0.98)	0.73 (0.43–1.25)	0.58 (0.34–0.99)	0.008
Total cardiovascular disease						
No. of cases	1220	125	78	61	67	
Age-adjusted relative risk (95% CI)	1.00	0.87 (0.72–1.04)	0.73 (0.58–0.92)	0.69 (0.53–0.89)	0.60 (0.47–0.76)	<0.001
Multivariate relative risk (95% CI)	1.00	0.91 (0.73–1.12)	0.81 (0.63–1.06)	0.85 (0.64–1.13)	0.76 (0.58–1.00)	0.01

*Coronary heart disease includes nonfatal myocardial infarction and fatal coronary disease. Multivariate models included age (as a continuous variable), smoking status (0, 1 to 14, 15 to 24, or ≥25 cigarettes per day), race or ethnic group (non-Hispanic white, non-Hispanic black, Hispanic, Asian, or other), level of education (5 categories), family income (7 categories), body-mass index (<25.0, 25.0 to 29.9, or ≥30.0), waist-to-hip ratio (as a continuous variable), level of alcohol intake (0, 1 to 4, 5 to 14, or ≥15 g per day), parental history of premature myocardial infarction, age at menopause, use or nonuse of hormone-replacement therapy, percentage of calories from saturated fat, number of servings of fruit and vegetables per day, and dietary fiber intake (g per day). MET denotes metabolic equivalent, and CI confidence interval.

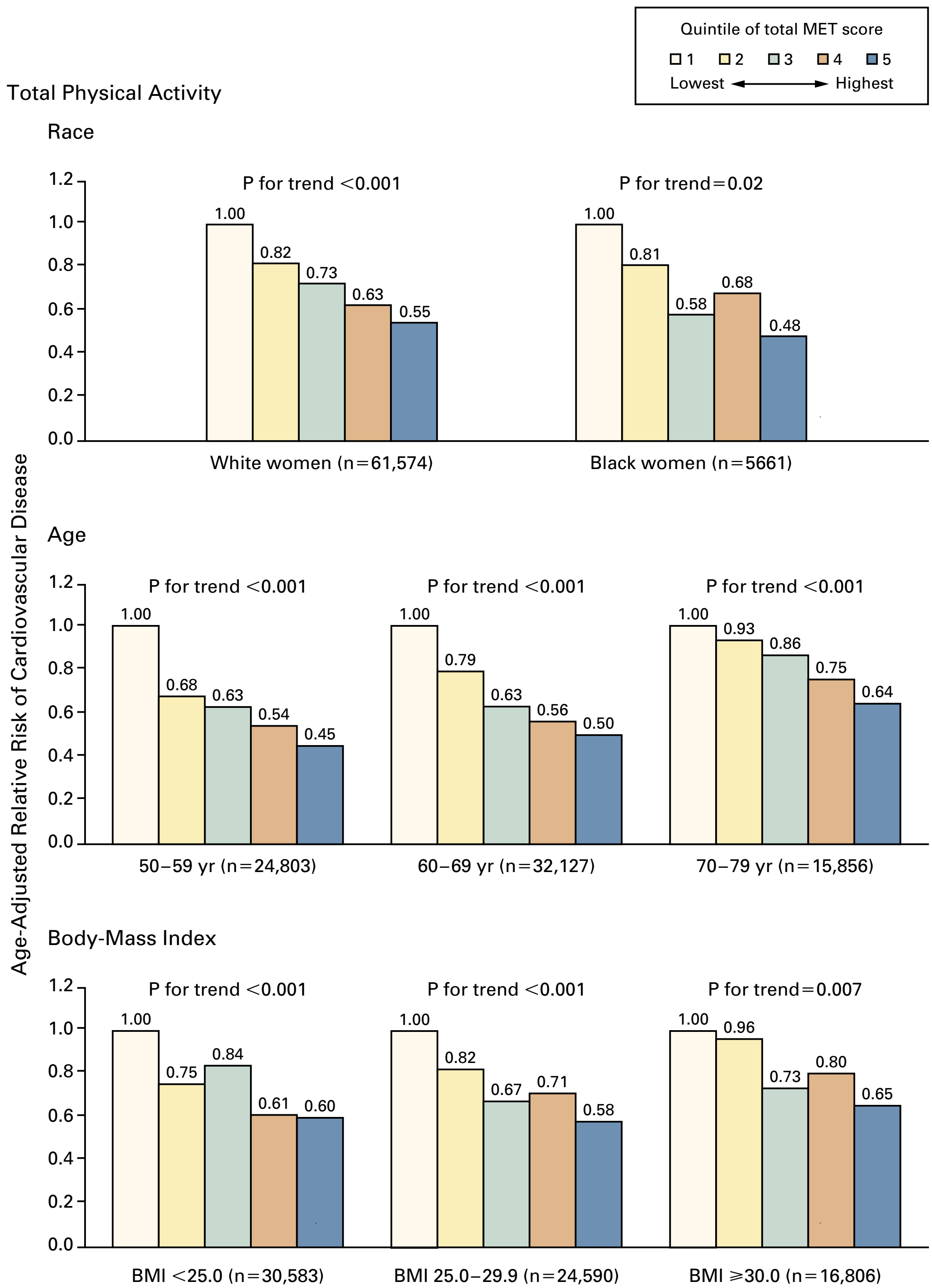

Figure 1. Age-Adjusted Relative Risks of Cardiovascular Disease According to Quintile of Total MET Score in Subgroups Defined by Race, Age, and Body-Mass Index (BMI).

The reference category is the lowest quintile of MET score.

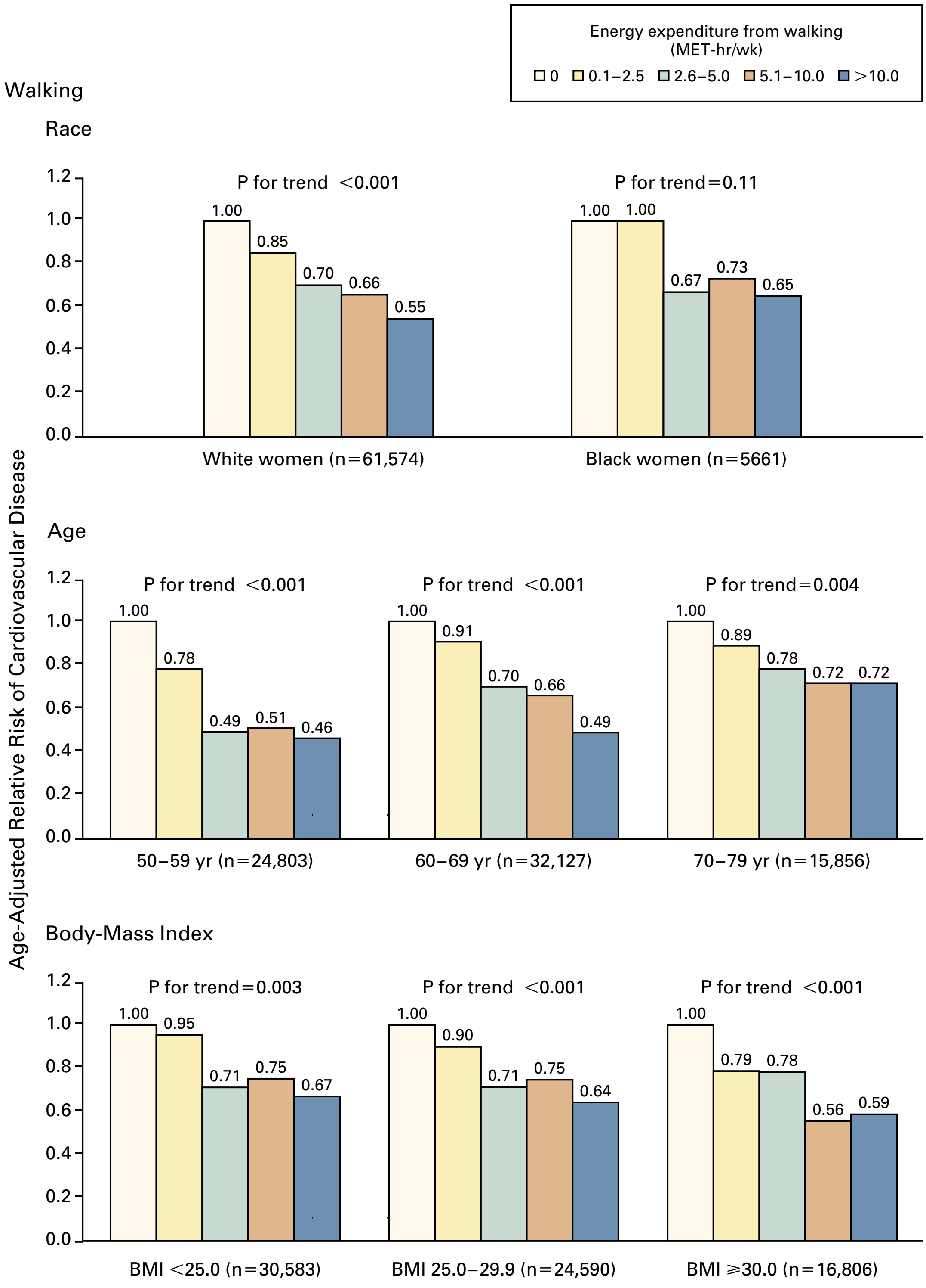

Figure 2. Age-Adjusted Relative Risks of Cardiovascular Disease According to Energy Expenditure from Walking (MET-Hr/Wk) in Subgroups Defined by Race, Age, and Body-Mass Index (BMI).

The reference category is the lowest category of energy expenditure from walking.

orous exercise (activities with MET scores of 6 or higher; P for trend = 0.008) (Table 1).

Reductions in the risk of total cardiovascular events with increasing categories of total MET scores, walking, and vigorous exercise were similar to those for the risk of coronary disease (Table 1). Women who either walked or exercised vigorously at least 2.5 hours per week had a risk reduction of approximately 30 percent. Similar reductions in the risk of cardiovascular events with an increasing MET score were observed for white women and for black women (for other racial and ethnic groups, the samples were not large enough to be analyzed separately), as well as for women in different categories of age or body-mass index (Fig. 1). The relative risk of cardiovascular disease in the highest quintile of MET score as compared with the lowest quintile was 0.55 (95 percent confidence interval, 0.47 to 0.65) among white women and 0.48 (95 percent confidence interval, 0.25 to 0.93) among black women. Moreover, increasing categories of walking were inversely associated with the risk of cardiovascular events in each of these subgroups (Fig. 2). Women who engaged in both walking and vigorous exercise had greater reductions in cardiovascular risk than those who did either one alone (the age-adjusted relative risk for those in the highest category of each was 0.37 [95 percent confidence interval, 0.25 to 0.57]) (Fig. 3).

In multivariate analyses, after simultaneous control for age, race or ethnic group, smoking status, body-mass index, waist-to-hip ratio, socioeconomic status, several dietary factors, and other covariates, physical activity remained a powerful predictor of the subsequent risk of cardiovascular events (Table 1). For increasing quintiles of the total MET score, the relative risks were 1.00, 0.89, 0.81, 0.78, and 0.72, respectively (P for trend <0.001). Increasing categories of walking were associated with similar reductions in risk (relative risks, 1.00, 0.91, 0.82, 0.75, and 0.68, respectively; P for trend <0.001), which were also similar to the risk reductions with vigorous exercise (Table 1) and remained unchanged after simultaneous inclusion of walking and vigorous exercise in the model. These results were not substantially altered after further control for biologic variables that could be considered to be in the causal pathway, such as hypertension, hypercholesterolemia, and diabetes, and for the summary score for mental and emotional health[13] (the relative risks of cardiovascular events with increasing total MET scores were 1.00, 0.92, 0.87, 0.83, and 0.77, respectively; P for trend = 0.008). When we excluded data from the first year of follow-up (to minimize potential bias caused by the influence of subclinical disease on the activity level), the results were not materially altered (the multivariate relative risk of car-

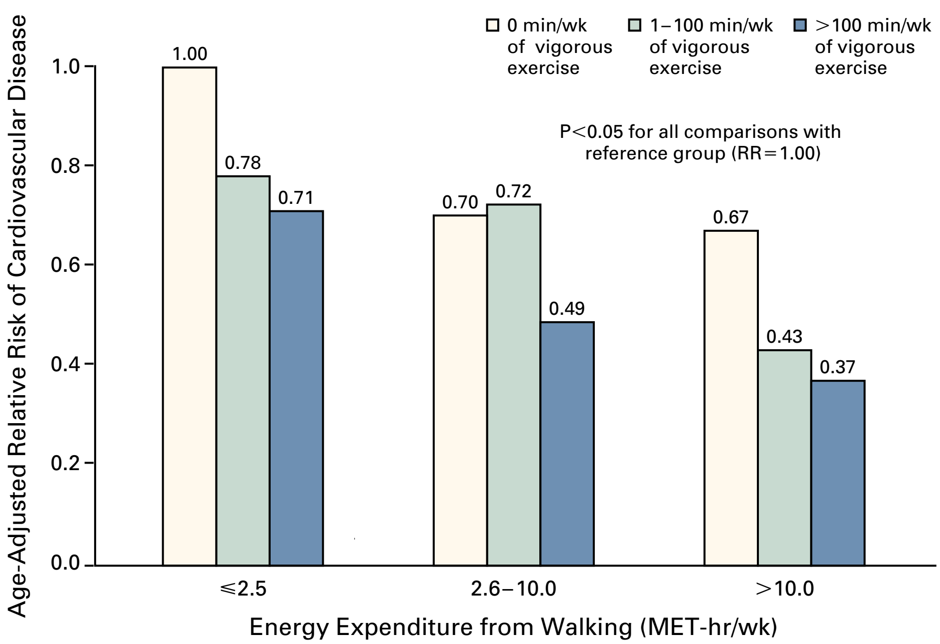

Figure 3. Joint Association of Walking and Vigorous Exercise with the Age-Adjusted Relative Risk of Cardiovascular Disease. RR denotes relative risk.

diovascular disease for women in the highest quintile of total MET score was 0.76 [95 percent confidence interval, 0.61 to 0.96; P for trend = 0.02]).

Walking pace was also an important determinant of reduction in cardiovascular risk (Fig. 4). As compared with women who never or rarely walked (the reference category, with a relative risk of 1.00), women who walked at faster paces of 2 to 3 miles per hour (mph) (3.2 to 4.8 km per hour), 3 to 4 mph (4.8 to 6.4 km per hour), and more than 4 mph had relative risks of cardiovascular disease of 0.86, 0.76, and 0.58, respectively (P for trend = 0.002), according to multivariate models that included control for time spent walking.

Finally, we assessed the relation between hours spent sitting, as well as hours spent lying down or sleeping, and the risk of cardiovascular events. After we accounted for age and recreational energy expenditure (total MET score), the relative risk of cardiovascular disease was 1.38 (95 percent confidence interval, 1.01 to 1.87) among women who spent 12 to 15 hours per day lying down or sleeping and 1.68 (95 percent confidence interval, 1.07 to 2.64) among women who spent at least 16 hours per day sitting, as compared with those who spent less than 4 hours per day. Other durations of sitting or lying down were not significantly associated with cardiovascular risk.

DISCUSSION

These prospective data from an ethnically diverse cohort of postmenopausal women indicate that both walking and vigorous exercise are associated with substantial reductions in the incidence of cardiovascular events. In contrast, prolonged time spent sitting predicts increased risk. We observed similar magnitudes of risk reduction with walking and vigorous exercise, and the results were similar among white women and black women as well as among women in different age groups and categories of body-mass index. These findings extend those of previous analyses from predominantly white populations[14-17] to a racially and ethnically diverse cohort of women in the United States. The results also lend further support to current federal exercise guidelines that endorse moderate-inten-

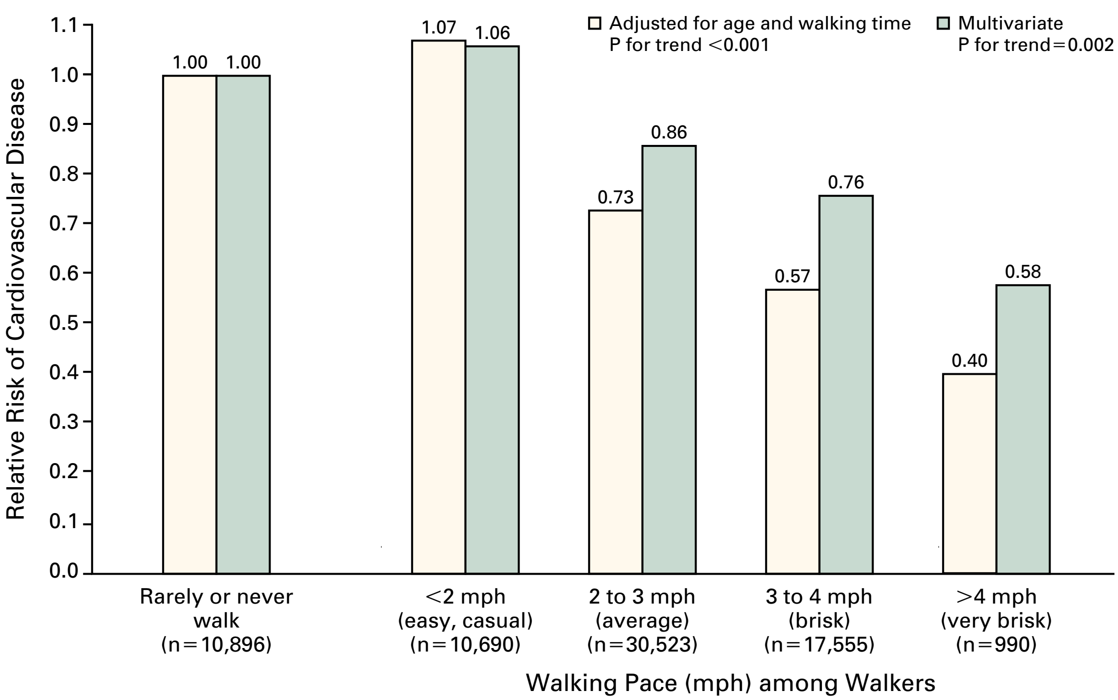

Figure 4. Multivariate Relative Risk of Cardiovascular Disease and Relative Risk Adjusted for Age and Walking Time, According to Walking Pace.

Multivariate relative risks were adjusted for age, time spent walking, smoking status (0, 1 to 14, 15 to 24, or ≥25 cigarettes per day), race or ethnic group, level of education, annual family income, body-mass index, waist-to-hip ratio, level of alcohol intake, parental history of premature myocardial infarction, age at menopause, use or nonuse of hormone-replacement therapy, percentage of calories from saturated fat, number of servings of fruit and vegetables per day, and dietary fiber intake. To convert values for distance to kilometers, multiply by 1.6.

sity exercise for at least 30 minutes on most, and preferably all, days of the week.[3,4] Women who either walked briskly or exercised vigorously at least 2.5 hours per week had a risk reduction of approximately 30 percent. Evidence of the applicability of these guidelines to nonwhite women is of particular importance because of the high prevalence of sedentary lifestyles, obesity, and related conditions in minority populations.[3]

Strengths of the present study include the prospective design, the large size, the racial and ethnic diversity of the cohort, the detailed assessment of physical activity as well as sedentary behavior, and the uniform and strict criteria for the coronary and cardiovascular end points. Women with diagnosed cardiovascular disease or cancer at base line and those who were nonambulatory (unable to walk at least one block) were excluded from the analyses. These exclusions and the prospective design minimized any influence of preexisting disease on the level of physical activity. Moreover, we performed secondary analyses excluding data from the first year of follow-up in order to minimize bias related to the presence of subclinical disease. The strong dose–response gradient observed between the physical-activity level and the reduced risk of cardiovascular disease and the consistency of the findings across strata of age, race, and body-mass index lend further credence to a causal interpretation. Other strengths of the study include the high follow-up rate and the detailed information about potential confounding variables.

Because our multivariate analyses controlled for several factors that could be considered to be intermediate biologic variables,[3] such as body-mass index and waist-to-hip ratio, and additional models controlled for history of hypertension, hypercholesterolemia, and diabetes, our analyses provide a conservative estimate of the relation between activity and cardiovascular disease. Physical activity may be associated with even greater reductions in cardiovascular risk — closer to the 50 percent reductions found in our age-adjusted analyses — given that the relative risks derived from the multivariate models estimate the effects of exercise without taking into account its favorable influence on adiposity and related morbidity.

Some limitations of our study also deserve attention. Physical activity was assessed by questionnaire, and some misclassification of exposure was inevitable. Nondifferential misclassification of exposure, however, would be expected to bias the risk estimate toward unity; thus, it cannot explain the strong inverse associations observed between the level of physical activity and the incidence of cardiovascular events. Despite the fact that we controlled for a large number of potentially confounding variables in our multivariate analyses, residual confounding by lifestyle-related factors cannot be excluded. Finally, our study population of volunteers in the Women's Health Initiative, although of more diverse racial and ethnic background and socioeconomic status than most previously studied cohorts, is not an entirely representative cross-section of women in the United States.

More than 40 epidemiologic studies have addressed the relation between exercise and cardiovascular disease,[1,2] but only one third of published studies have included women,[14-28] and few of these have specifically addressed the role of walking.[14-19] In previous studies, results for women have been generally similar to those for men, indicating that risk among both sexes is reduced by 30 to 50 percent with regular physical activity. Recent reports from several large-scale cohort studies involving women[14,15,20] have suggested that moderate and vigorous exercise have similar cardiovascular benefits, but these cohorts were predominantly white. Moreover, to our knowledge, no previous large-scale study has addressed the relation between walking and cardiovascular events in black women or the role of sitting after accounting for recreational energy expenditure in women. The evidence that moderate-intensity activity is associated with a similar magnitude of reduction in cardiovascular risk among white women and black women, among younger and older postmenopausal women, and across the spectrum of adiposity is important for the targeting of these diverse groups with health-promotion activities. The cardiovascular benefits of walking[29] and even moderate levels of physical fitness[27,30] also appear to apply to men.

An important role for both moderate and vigorous exercise in reducing cardiovascular risk is also biologically plausible. Increasing intensity or duration of exercise has a graded relation to improvements in lipid levels[3,31] and insulin sensitivity.[32] Moderate-intensity activity may produce reductions in diastolic blood pressure similar to those achieved with vigorous exercise and may produce even greater reductions in systolic blood pressure.[3] Moderate exercise coupled with modification of the diet led to a reduced risk of type 2 diabetes among subjects with impaired glucose tolerance.[33,34] Moreover, equivalent energy expenditure with moderate or vigorous exercise leads to similar reductions in adipose mass.[3] Finally, physical activity of any intensity has been linked to improvement in emotional well-being.[3]

In conclusion, these prospective data from a large and diverse cohort of postmenopausal women indicate that both walking and vigorous exercise are associated with substantial reductions in the risk of cardiovascular events. A graded inverse relation was observed among both white women and black women, lean women and obese women, and younger women and older women. Moreover, prolonged time spent sitting predicted increased risk. These findings lend support to current federal guidelines that endorse moderate-intensity activity, including walking. Although vigorous exercise should not be discouraged for those who choose a higher intensity of activity, our results indicate that moderate-intensity exercise confers substantial health benefits for postmenopausal women.

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APPENDIX

The following persons are members of the Women's Health Initiative Study Group. *Program office:* J.E. Rossouw, L. Pottern, S. Ludlam, J. McGowan, N. Morris (National Heart, Lung, and Blood Institute, Bethesda, Md.). *Clinical coordinating center:* R. Prentice, G. Anderson, A. LaCroix, R. Patterson, A. McTiernan (Fred Hutchinson Cancer Research Center, Seattle); S. Shumaker, P. Rautaharju (Bowman Gray School of Medicine, Winston-Salem, N.C.); E. Stein (Medical Research Labs, Highland Heights, Ky.); S. Cummings (University of California at San Francisco, San Francisco); J. Himes (University of Minnesota, Minneapolis); S. Heckbert (University of Washington, Seattle). *Clinical centers:* S. Wassertheil-Smoller (Albert Einstein College of Medicine, Bronx, N.Y.); J. Hays (Baylor College of Medicine, Houston); J. Manson (Brigham and Women's Hospital and Harvard Medical School, Boston); A.R. Assaf (Brown University, Providence, R.I.); L. Phillips (Emory University, Atlanta); S. Beresford (Fred Hutchinson Cancer Research Center, Seattle); J. Hsia (George Washington University Medical Center, Washington, D.C.); C. Ritenbaugh (Kaiser Permanente Center for Health Research, Portland, Oreg.); B. Caan (Kaiser Permanente Division of Research, Oakland, Calif.); J. Morley Kotchen (Medical College of Wisconsin, Milwaukee); B.V. Howard (Medstar Research Institute, Washington, D.C.); L. Van Horn (Northwestern University, Chicago and Evanston, Ill.); H. Black (Rush–Presbyterian–St. Luke's Medical Center, Chicago); M.L. Stefanick (Stanford Center for Research in Disease Prevention, Stanford University, Stanford, Calif.); D. Lane (State University of New York at Stony Brook, Stony Brook); R. Jackson (Ohio State University, Columbus); C.B. Lewis (University of Alabama at Birmingham, Birmingham); T. Bassford (University of Arizona, Tucson and Phoenix); M. Trevisan (State University of New York at Buffalo, Buffalo); J. Robbins (University of California at Davis, Sacramento); A. Hubbell (University of California at Irvine, Orange); H. Judd (University of California at Los Angeles, Los Angeles); R.D. Langer (University of California at San Diego, LaJolla and Chula Vista); M. Gass (University of Cincinnati, Cincinnati); M. Limacher (University of Florida, Gainesville and Jacksonville); D. Curb (University of Hawaii, Honolulu); R. Wallace (University of Iowa, Iowa City and Davenport); J. Ockene (University of Massachusetts, Worcester); N. Lasser (University of Medicine and Dentistry of New Jersey, Newark); M.J. O'Sullivan (University of Miami, Miami); K. Margolis (University of Minnesota, Minneapolis); R. Brunner (University of Nevada, Reno); G. Heiss (University of North Carolina, Chapel Hill); L. Kuller (University of Pittsburgh, Pittsburgh); K.C. Johnson (University of Tennessee, Memphis); R. Schenken (University of Texas Health Science Center, San Antonio); C. Allen (University of Wisconsin, Madison); G. Burke (Wake Forest University School of Medicine, Winston-Salem, N.C.); S. Hendrix (Wayne State University School of Medicine and Hutzel Hospital, Detroit).

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