JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 14, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.08.017

ORIGINAL INVESTIGATIONS

# Physical Activity and Mortality in Patients With Stable Coronary Heart Disease

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## ABSTRACT

**BACKGROUND** Recommendations for physical activity in patients with stable coronary heart disease (CHD) are based on modest evidence.

**OBJECTIVES** The authors analyzed the association between self-reported exercise and mortality in patients with stable CHD.

**METHODS** A total of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) study completed questions at baseline on hours spent each week taking mild, moderate, and vigorous exercise. Associations between the volume of habitual exercise in metabolic equivalents of task hours/week and adverse outcomes during a median follow-up of 3.7 years were evaluated.

**RESULTS** A graded decrease in mortality occurred with increased habitual exercise that was steeper at lower compared with higher exercise levels. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for covariates, HR: 0.90; 95% CI: 0.87 to 0.93). These associations were similar for cardiovascular mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96), but myocardial infarction and stroke were not associated with exercise volume after adjusting for covariates. The association between decrease in mortality and greater physical activity was stronger in the subgroup of patients at higher risk estimated by the ABC-CHD (Age, Biomarkers, Clinical-Coronary Heart Disease) risk score (p for interaction = 0.0007).

**CONCLUSIONS** In patients with stable CHD, more physical activity was associated with lower mortality. The largest benefits occurred between sedentary patient groups and between those with the highest mortality risk. (J Am Coll Cardiol 2017;70:1689–700) © 2017 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**CABG** = coronary artery bypass graft

**CHD** = coronary heart disease

**CI** = confidence interval

**CV** = cardiovascular

**eGFR** = estimated glomerular filtration rate

**HDL** = high-density lipoprotein

**HR** = hazard ratio

**LDL** = low-density lipoprotein

**METs** = metabolic equivalents

**MI** = myocardial infarction

Clinical practice guidelines for prevention of cardiovascular (CV) disease recommend ≥150 min of moderate intensity or ≥60 to 75 min of vigorous exercise each week (1-3). Guidelines on secondary prevention of stable coronary heart disease (CHD) have recommended similar levels of regular moderate or vigorous exercise (4,5). These recommendations are based in part on studies that indicate cardiorespiratory fitness predicts mortality, and regular moderate or vigorous exercise improves physical fitness more than mild intensity exercise does (6). Most information on the relationship between physical activity and mortality comes from large general population studies (7-9). These studies suggest that there is a graded association between a combination of the intensity and duration of self-reported regular exercise and mortality, even at levels below those recommended in current guidelines (1-3). Milder intensity exercise, less sedentary time, and more time spent standing are also associated with lower mortality in general population cohorts (10,11).

Few studies have evaluated the potential benefits of lower intensity exercise in CHD populations, although several have evaluated more vigorous exercise (12,13). Runners with a history of myocardial infarction (MI) have lower mortality than nonrunners, but very high durations and intensities of running may increase CV risk (13). Randomized clinical trials of exercise training after MI suggest that increasing exercise lowers CV risk (14). However, these trials provide limited evidence on the importance of the intensity and duration of exercise interventions for prognosis; most studies were small, and reporting of exercise interventions was often poor (15).

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We analyzed relationships between the amount of mild, moderate, and vigorous physical activity assessed by self-reported questionnaire (16) and

Trials, French Clinical Research Infrastructure Network, Institut National de la Santé et de la Recherche Mèdicale U1148, Paris, France. The STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial and the lifestyle substudy were funded by GlaxoSmithKline. The charge for Open Access has been paid by GlaxoSmithKline. Drs. Stewart, Held, Vedin, Hagström, Lonn, Armstrong, Granger, Hochman, Wallentin, and White are STABILITY Study Investigators. Dr. Stewart has received grants and nonfinancial support from GlaxoSmithKline. Dr. Held has received an institutional research grant and Speakers Bureau honoraria from AstraZeneca; and institutional research grants from Bristol-Myers Squibb, Pfizer, Merck & Co., GlaxoSmithKline, and Roche. Mr. Hadziosmanovic has received grants from GlaxoSmithKline. Dr. Armstrong has received grants and personal fees from Merck & Co. and Bayer; grants from Sanofi; and personal fees from AstraZeneca, Axio/Orexigen, Eli Lilly, and Mast Therapeutics. Dr. Cannon has received research grants and consulting fees from Arisaph, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Merck & Co., Takeda; research grants from Janssen; and consulting fees from Alnylam, Amgen, Boehringer Ingelheim, Eli Lilly, Kowa, Lipimedix, Pfizer, Regeneron, and Sanofi. Dr. Granger has received grants and personal fees from Bristol-Myers Squibb, Pfizer, Bayer, Daiichi-Sankyo, Boehringer Ingelheim, Janssen, AstraZeneca, GlaxoSmithKline, The Medicines Company, and Novartis; grants from Armetheon, Medtronic Foundation, U.S. Food and Drug Administration; and personal fees from Eli Lilly, Gilead, Hoffmann-La Roche, Medtronic Inc., National Institutes of Health, and Verseon. Dr. Hagström has received institutional research grants from GlaxoSmithKline, AstraZeneca, Amgen, Sanofi, and Ariad; has served as an expert committee member for Sanofi and Amgen; has received lecture fees and institutional research grants from Sanofi and Amgen; has received institutional research grants from AstraZeneca and GlaxoSmithKline; and has served as an expert committee member for Ariad and Merck Sharp & Dohme. Dr. Hochman has received travel reimbursement from GlaxoSmithKline; a grant for the ISCHEMIA trial from National Institutes of Health; and support for drug distribution related to the ISCHEMIA trial from AstraZeneca. Dr. Koenig has received lecture and consultancy fees from Novartis, Amgen, and AstraZeneca; lecture fees from Actavis and Berlin-Chemie; consultancy fees from GlaxoSmithKline, The Medicines Company, Pfizer, DalCor, Merck Sharp & Dohme, and Kowa; and research grants from Roche Diagnostics, Abbott, Singulex, and Beckmann. Dr. Lonn has received institutional research grants from GlaxoSmithKline, during the conduct of the study; and institutional research grants from AstraZeneca, Hoffmann-La Roche, Novartis, Eli Lilly, Amgen, and Bayer. Dr. Nicolau has received grant support from Eli Lilly, AstraZeneca, Johnson & Johnson, Bristol-Myers Squibb, Astellas, Sanofi, and Daiichi-Sankyo; has received grant support and personal fees from GlaxoSmithKline, during the conduct of the study; has served as a board member for AstraZeneca, Bayer, and Sanofi; and has received lecture fees from AstraZeneca, Bayer, and Sanofi. Dr. Steg has received personal fees from GlaxoSmithKline, Amarin, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, The Medicines Company, CLS-Behring, and Janssen; grants, institutional research grants, personal fees, honoraria, and nonfinancial support from Sanofi and Servier; honoraria from Amgen and Regeneron; and personal fees, honoraria, and nonfinancial support from AstraZeneca. Dr. Vedin has received institutional research grants from GlaxoSmithKline; and lecture fees from Fresenius and Novartis. Dr. Wallentin has received institutional research grants, consultancy fees, lecture fees, and travel support from Bristol-Myers Squibb, Pfizer, AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim; institutional research grants from Merck & Co. and Roche; consultancy fees from Abbott; and holds two patents involving GDF-15 proteins. Dr. White has received research grants and personal fees from GlaxoSmithKline; research grants and advisory board member fees from AstraZeneca; advisory board member fees from Acetelion and Sirtex; research grants from Sanofi, Eli Lilly, National Institute of Health, Merck Sharp & Dohme, George Institute, Omthera Pharmaceuticals, Pfizer New Zealand, Intarcia Therapeutics Inc., Elsai Inc., Dal-GenE, and Daiichi-Sankyo Pharma Development. Paul Thompson, MD, served as Guest Editor for this paper.

Manuscript received April 18, 2017; revised manuscript received August 3, 2017, accepted August 4, 2017.

subsequent all-cause mortality, CV mortality, non-CV mortality, MI, and stroke in a large cohort of patients with stable CHD who participated in the global STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial (17).

## METHODS

**STUDY POPULATION.** STABILITY was a global outcomes trial designed to determine whether darapladib, a specific inhibitor of lipoprotein associated phospholipase $A_2$, would reduce risk of CV death, MI, and stroke in patients with chronic CHD (18). Subjects from 39 countries (n = 15,828) were randomized. All patients had chronic stable CHD, defined as prior MI (>1 month before randomization), prior percutaneous coronary intervention, coronary artery bypass graft (CABG), or multivessel CHD confirmed by coronary angiography. In addition, patients had to meet at least 1 of the following CV risk criteria: age ≥60 years; diabetes mellitus requiring pharmacotherapy; high-density lipoprotein (HDL)-cholesterol <1.03 mmol/l; current or previous smoker defined as ≥5 cigarettes per day on average; significant renal dysfunction (estimated glomerular filtration rate [eGFR]: ≥30 and <60 ml/min/1.73 $m^2$ or urine albumin-creatinine ratio ≥30 mg albumin/g creatinine); or polyvascular disease (CHD and cerebrovascular disease or CHD and peripheral arterial disease). Detailed descriptions of the study design and population have been published previously (18,19).

**PHYSICAL ACTIVITY.** At baseline, patients underwent a detailed medical history, physical examination, and fasting blood samples, and they were invited to complete a lifestyle questionnaire. Questions related to physical activity (based on the International Physical Activity Questionnaire [20]), were completed by 15,486 subjects (97.8%). Each subject was asked "How many hours during a typical week do you spend doing the following activities for 10 minutes or more? Please estimate to the nearest 1 h for each category: 1) Doing MILD physical activity such as easy walking, yoga, Tai Chi, mild house work? 2) Doing MODERATE physical activity such as fast walking, jogging, aerobics, gardening, bicycling, dancing, swimming or house cleaning? 3) Doing VIGOROUS exercise such as running, lifting heavy objects, playing strenuous sports or strenuous work?" Each level of exercise includes a range of intensities estimated to be <3 metabolic equivalents (METs) for task for mild, 3 to 6 METs for moderate, and >6 METs for vigorous intensity physical activity (21). To estimate the METs h/week, 2 METs were assigned for mild, 4 METs for moderate, and 8 METs for vigorous intensity activity, as previously reported (16). The average intensity of physical activity was calculated by dividing the total METs h/week by the total hours of exercise per week. The baseline characteristics of the study population have been described by tertile of self-reported physical activity previously (16).

Additionally, participants were asked "How active are you at work and during leisure time? At work (check 1) 'mainly sedentary,' 'predominantly walking on 1 level, no heavy lifting,' 'mainly walking, including climbing stairs, or walking uphill or lifting heavy objects,' 'heavy physical activity,' or 'I do not work.' During your leisure time (check 1) 'mainly sedentary,' 'mild exercise,' 'moderate exercise,' or 'strenuous physical exercise.'"

**CLINICAL OUTCOMES.** The primary endpoint was all-cause mortality. Secondary endpoints were CV death, MI, stroke, non-CV mortality, and major adverse coronary events defined as first occurrence of CV death, or stroke. For 90 deaths that occurred outside the period defined for evaluation of darapladib treatment, the cause of death was not defined. All other events were independently reviewed by an adjudication committee who had no knowledge of physical activity data. Event definitions and main results of the study have been presented elsewhere (17).

**STATISTICAL ANALYSIS.** The baseline characteristics of the study population were summarized by physical activity tertiles, with categorical variables presented as counts with proportions and continuous variables as medians and interquartile ranges. To investigate differences across the 3 groups of patients, categorical variables were compared with the chi-square test. Continuous variables were compared with Mann-Whitney nonparametric tests.

The associations between self-reported exercise and study outcomes were assessed using Cox proportional hazards regression models and expressed with hazard ratios (HRs) and 95% confidence intervals (CIs). In the multivariate model, we adjusted for randomized treatment, age, body mass index, sex, systolic blood pressure, hypertension, geographic region for final reporting, prior MI, prior percutaneous coronary intervention or CABG, prior multivessel CHD, baseline history of diabetes, smoking, polyvascular disease, significant renal dysfunction, hemoglobin, white blood cell count, low-density lipoprotein (LDL)-cholesterol, HDL-cholesterol, triglycerides, eGFR according to CKD-EPI (Chronic Kidney Disease Epidemiology research group) calculator, and history of congestive heart failure at baseline.

HR for change in different measures of self-reported physical activity were also analyzed. Spline plots were

**TABLE 1 Baseline Characteristics of Study Population by Physical Activity Tertile**

| | All Subjects (N = 15,487) | Least Active (n = 5,281) | Intermediate Activity (n = 5,055) | Most Active (n = 5,151) | p Value |
|---|---|---|---|---|---|
| Age, yrs | 65.0 ± 12.0 | 65.0 ± 12.0 | 65.0 ± 11.0 | 64.0 ± 12.0 | <0.0001 |
| Female | 2,885 (18.6) | 921 (17.4) | 989 (19.6) | 975 (18.9) | 0.0170 |
| Time from qualifying event to randomization, yrs | 3.42 ± 6.38 | 3.22 ± 6.32) | 3.49 ± 6.66 | 3.57 ± 6.25 | <0.0001 |
| Follow-up time from randomization, yrs | 3.79 ± 0.31 | 3.75 ± 0.32 | 3.80 ± 0.31 | 3.81 ± 0.31 | <0.0001 |
| Attended cardiac rehabilitation | 5,397 (35.1) | 1,608 (30.7) | 1,865 (37.2) | 1,924 (37.6) | <0.0001 |
| Geographic region | | | | | |
| Asia/Pacific | 3,052 (19.7) | 1,275 (24.1) | 1,054 (20.9) | 723 (14.0) | <0.0001 |
| Eastern Europe | 3,442 (22.2) | 805 (15.2) | 1,107 (21.9) | 1,530 (29.7) | <0.0001 |
| North America | 3,969 (25.6) | 1,397 (26.5) | 1,323 (26.2) | 1,249 (24.2) | <0.0001 |
| South America | 1,177 (7.6) | 646 (12.2) | 320 (6.3) | 211 (4.1) | <0.0001 |
| Western Europe | 3,847 (24.8) | 1,158 (21.9) | 1,251 (24.7) | 1,438 (27.9) | <0.0001 |
| Risk factors | | | | | |
| Current smoker | 2,789 (18.0) | 938 (17.8) | 813 (16.1) | 1,038 (20.2) | <0.0001 |
| Body mass index, kg/m$^2$ | 28.3 ± 6.2 | 28.4 ± 6.9 | 28.2 ± 6.0 | 28.3 ± 5.8 | 0.0066 |
| Systolic blood pressure, mm Hg | 131.0 ± 22.0 | 130.0 ± 23.0 | 130.0 ± 22.0 | 131.0 ± 22.0 | 0.0100 |
| Diastolic blood pressure, mm Hg | 79.0 ± 13.0 | 78.0 ± 14.0 | 79.0 ± 14.0 | 80.0 ± 13.0 | <0.0001 |
| Hypertension | 11,075 (71.5) | 3,854 (73.0) | 3,579 (70.8) | 3,642 (70.7) | 0.0144 |
| LDL-cholesterol, mmol/l | 2.07 ± 0.99 | 2.01 ± 1.01 | 2.06 ± 0.96 | 2.14 ± 1.00 | <0.0001 |
| HDL-cholesterol, mmol/l | 1.15 ± 0.38 | 1.13 ± 0.40 | 1.17 ± 0.40 | 1.19 ± 0.40 | <0.0001 |
| Triglycerides, mmol/l | 1.52 ± 1.03 | 1.58 ± 1.03 | 1.50 ± 1.02 | 1.46 ± 1.02 | <0.0001 |
| HB, g/l | 144.0 ± 18.0 | 142.0 ± 19.0 | 144.0 ± 18.0 | 145.0 ± 17.0 | <0.0001 |
| WBC, gi/l | 6.5 ± 2.3 | 6.7 ± 2.4 | 6.5 ± 2.2 | 6.4 ± 2.2 | <0.0001 |
| eGFR (according to CKD-EPI) | 74.4 ± 25.1 | 72.9 ± 27.6 | 73.9 ± 24.5 | 75.8 ± 23.1 | <0.0001 |
| Diabetes mellitus | 6,000 (38.7) | 2,297 (43.5) | 1,965 (38.9) | 1,738 (33.7) | <0.0001 |
| Cardiovascular and renal disease markers | | | | | |
| Significant renal dysfunction | 4,682 (30.2) | 1,828 (34.6) | 1,557 (30.8) | 1,297 (25.2) | <0.0001 |
| Prior myocardial infarction | 9,114 (58.8) | 3,156 (59.8) | 2,907 (57.5) | 3,051 (59.2) | 0.0528 |
| Prior PCI or CABG | 11,610 (75.0) | 3,881 (73.5) | 3,855 (76.3) | 3,874 (75.2) | 0.0045 |
| Multivessel coronary heart disease | 2,337 (15.1) | 918 (17.4) | 711 (14.1) | 708 (13.7) | <0.0001 |
| Polyvascular disease | 2,325 (15.0) | 829 (15.7) | 759 (15.0) | 737 (14.3) | 0.1389 |
| Congestive heart failure | 3,326 (21.5) | 1,139 (21.6) | 1,087 (21.5) | 1,100 (21.4) | 0.9628 |
| STABILITY CHD risk score | 0.44 ± 0.76 | 0.50 ± 0.99 | 0.44 ± 0.76 | 0.39 ± 0.62 | <0.0001 |
| Measures of physical activity | | | | | |
| All self-reported physical activity, METs h/week | 40.0 ± 52.0 | 14.0 ± 12.0 | 40.0 ± 14.0 | 90.0 ± 52.0 | <0.0001 |
| Duration of physical activity, h/week | 14.0 ± 16.0 | 5.0 ± 4.0 | 14.0 ± 7.0 | 28.0 ± 13.0 | <0.0001 |
| Average exercise intensity, METs | 2.6 ± 1.2 | 1.9 ± 0.6 | 2.6 ± 0.9 | 3.2 ± 1.0 | <0.0001 |
| Mild exercise, h/week | 7.0 ± 10.0 | 4.0 ± 5.0 | 9.0 ± 8.0 | 14.0 ± 14.0 | <0.0001 |
| Moderate exercise, h/week | 4.0 ± 10.0 | 0.0 ± 2.0 | 4.0 ± 5.0 | 11.0 ± 12.0 | <0.0001 |
| Vigorous exercise, h/week | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 | 1.0 ± 5.0 | <0.0001 |
| Moderate or vigorous intensity exercise, METs h/week | 20.0 ± 48.0 | 0.0 ± 8.0 | 20.0 ± 20.0 | 64.0 ± 40.0 | <0.0001 |

*Continued on the next page*

constructed to show relations between self-reported exercise and mortality—all-cause, CV, and non-CV (22,23). Because the association between METs h/week and mortality was nonlinear (Online Figure 1), splines were also evaluated for the natural logarithm of physical activity volume (Online Figure 2). Subjects were grouped in increasing categories representing an approximate doubling of exercise volumes: 0; 0 to <5; 5 to <10; 10 to <20; 20 to <40; 40 to <80; 80 to <160; and >160 METs h/week.

Secondary analyses evaluated associations between physical activity and mortality in subgroups defined by baseline clinical characteristics and physical activity level. The ABC-CHD (Age, Biomarkers, Clinical-Coronary Heart Disease) risk score, which estimates the risk of CV death based on N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin T, LDL-cholesterol, smoking, diabetes mellitus, and peripheral arterial disease, was used to estimate overall CHD risk (24). The chi-square value minus degrees of freedom was used to compare the relative strength of association of all covariates with mortality (Online Figure 3). All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina). A 2-sided p value of <0.05 was considered statistically significant.

**TABLE 1 Continued**

| | All Subjects (N = 15,487) | Least Active (n = 5,281) | Intermediate Activity (n = 5,055) | Most Active (n = 5,151) | p Value |
|---|---|---|---|---|---|
| Highest reported intensity of habitual physical activity | | | | | |
| Mild | 3,755 (24.2) | 2,637 (50.6) | 1,038 (20.5) | 80 (1.6) | <0.0001 |
| Moderate | 7,511 (48.4) | 1,910 (36.2) | 3,099 (61.3) | 2,502 (48.6) | <0.0001 |
| Vigorous | 3,651 (23.6) | 164 (3.1) | 918 (18.1) | 2,569 (49.9) | <0.0001 |
| Physical activity during leisure time | | | | | |
| Mainly sedentary | 4,905 (32.5) | 2,509 (48.9) | 1,416 (28.8) | 980 (19.5) | <0.0001 |
| Mild exercise | 6,655 (44.2) | 2,126 (41.4) | 2,388 (48.5) | 2,141 (42.7) | <0.0001 |
| Moderate exercise | 3,377 (22.4) | 484 (9.4) | 1,089 (22.1) | 1,804 (36.0) | <0.0001 |
| Strenuous physical exercise | 136 (0.9) | 15 (0.3) | 32 (0.6) | 89 (1.8) | <0.0001 |
| Physical activity at work | | | | | |
| Mainly sedentary | 2,499 (16.4) | 1,157 (22.3) | 819 (16.5) | 523 (10.3) | <0.0001 |
| Predominantly walking on 1 level, no heavy lifting | 2,558 (16.8) | 856 (16.5) | 869 (17.6) | 833 (16.5) | <0.0001 |
| Mainly walking, including climbing stairs, or walking uphill or lifting heavy objects | 1,488 (9.8) | 316 (6.1) | 360 (7.3) | 812 (16.0) | <0.0001 |
| Heavy physical activity | 222 (1.5) | 32 (0.6) | 25 (0.5) | 165 (3.3) | <0.0001 |
| I do not work | 8,438 (55.5) | 2,832 (54.5) | 2,878 (58.1) | 2,728 (53.9) | <0.0001 |
| Symptoms that limit exercise | | | | | |
| Dyspnea | 7,692 (50.1) | 2,767 (52.9) | 2,505 (50.0) | 2,420 (47.3) | <0.0001 |
| Chest pain or discomfort | 5,751 (37.5) | 2,052 (39.3) | 1,890 (37.9) | 1,809 (35.4) | 0.0003 |
| Fatigue | 9,347 (61.1) | 3,226 (61.9) | 3,022 (60.7) | 3,099 (60.8) | 0.3459 |

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; CHD = coronary heart disease; CKD-EPI = Chronic Kidney Disease Epidemiology research group calculator; eGFR = estimated glomerular filtration rate; HB = hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; METs = metabolic equivalents; PCI = percutaneous coronary intervention; STABILITY = Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (trial); WBC = white blood cell count.

## RESULTS

**STUDY POPULATION.** Baseline characteristics of the study population are presented in Table 1. Participants in the most active tertile were less likely to have chronic renal disease, multivessel coronary artery disease, or diabetes. Patients from South America and Asia/Pacific were less active, and those from Eastern and Western Europe on average were more physically active. White blood cell count was lower, and hemoglobin, HDL-cholesterol, and eGFR were higher in the most active tertile. LDL-cholesterol was slightly higher and current smoking slightly more common in the most active group. More physical activity was associated with a lower ABC-CHD risk score.

For the least active tertile, the majority of exercise was of mild intensity and few subjects in this group reported more than 10 METs h/week of moderate or vigorous exercise each week (Table 1). Both the reported average exercise intensity and time spent exercising each week increased progressively from the least active to the intermediate and most active tertiles of physical activity. There were small differences in the proportion of subjects who reported at least some limitation of exercise by dyspnea and chest discomfort.

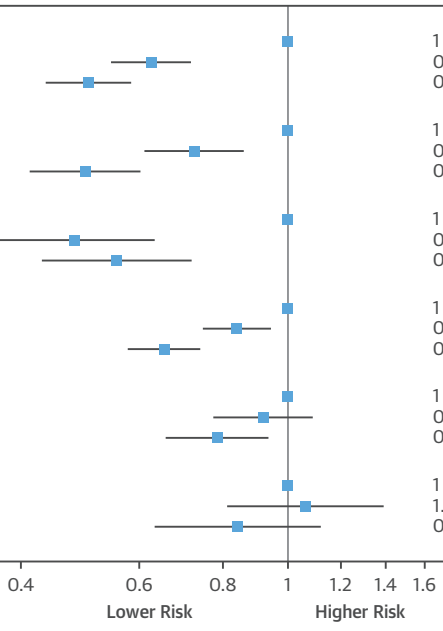
**OUTCOMES BY TERTILE OF PHYSICAL ACTIVITY.** Outcomes by physical activity tertile before and after adjusting for covariates are displayed in Figures 1A and 1B, respectively. There was a graded lower total, CV, and non-CV mortality with higher physical activity. Total mortality in the most active tertile was ~50% that of the least active tertile in the unadjusted model, and ~30% lower after adjusting for baseline covariates. Physical activity was associated with CV death and with major adverse CV events. The risk of MI was lower at higher physical activity before but not after adjusting for covariates. There was no significant association between stroke and exercise in either the unadjusted or fully adjusted models.

**VOLUME, INTENSITY, AND DURATION OF HABITUAL EXERCISE AND MORTALITY.** Doubling of exercise volume was associated with lower all-cause mortality both before (HR: 0.82; 95% CI: 0.79 to 0.85) and after adjusting for covariates (HR: 0.90; 95% CI: 0.87 to 0.93) (Central Illustration). The association between doubling of exercise volume was observed for both CV (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96) and non-CV mortality (unadjusted HR: 0.83; 95% CI: 0.78 to 0.88; adjusted HR: 0.88; 95% CI: 0.83 to 0.95) (Figure 2).

**FIGURE 1 HR for Outcomes for the Middle and Most Active Physical Activity Tertiles of the Study Population Compared With the Most Sedentary Tertile, Before and After Adjustment for Covariates**

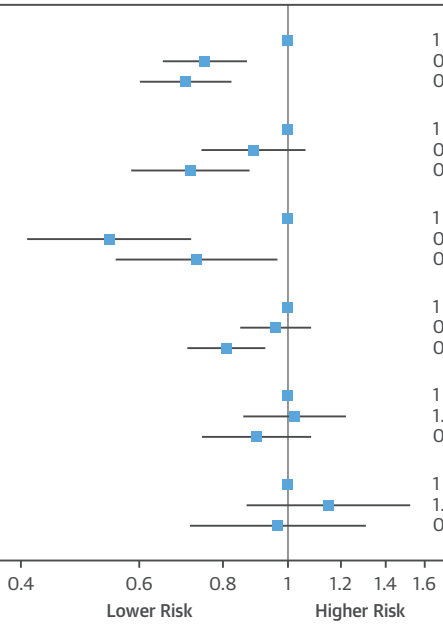
**A**

| Outcome Physical Activity | No of Patients | No of Events (%/3 yrs) | HR (95% CI) Least Active as Reference | p-value |
|---|---|---|---|---|
| **All-cause mortality** | | | | |
| Least Active | 5281 | 528 (8.72) | 1 | |
| Intermediate activity | 5055 | 326 (5.47) | 0.62 (0.54-0.72) | |
| Most Active | 5151 | 273 (4.45) | 0.50 (0.44-0.58) | <0.0001 |
| **CV death** | | | | |
| Least Active | 5281 | 320 (5.29) | 1 | |
| Intermediate activity | 5055 | 229 (3.84) | 0.72 (0.61-0.86) | |
| Most Active | 5151 | 162 (2.64) | 0.50 (0.41-0.60) | <0.0001 |
| **Non-CV death** | | | | |
| Least Active | 5281 | 159 (2.63) | 1 | |
| Intermediate activity | 5055 | 76 (1.28) | 0.48 (0.37-0.63) | |
| Most Active | 5151 | 91 (1.49) | 0.56 (0.43-0. 72) | <0.0001 |
| **MACE** | | | | |
| Least Active | 5281 | 621 (10.61) | 1 | |
| Intermediate activity | 5055 | 515 (8.91) | 0.84 (0.75-0.94) | |
| Most Active | 5151 | 413 (6.93) | 0.65 (0.58-0.74) | <0.0001 |
| **MI** | | | | |
| Least Active | 5281 | 277 (4.70) | 1 | |
| Intermediate activity | 5055 | 251 (4.31) | 0.92 (0.77-1.09) | |
| Most Active | 5151 | 220 (3.67) | 0.78 (0.66-0.94) | 0.0255 |
| **Stroke** | | | | |
| Least Active | 5281 | 104 (1.73) | 1 | |
| Intermediate activity | 5055 | 109 (1.84) | 1.06 (0.81-1.39) | |
| Most Active | 5151 | 89 (1.46) | 0.84 (0.63-1.12) | 0.2498 |




**B**

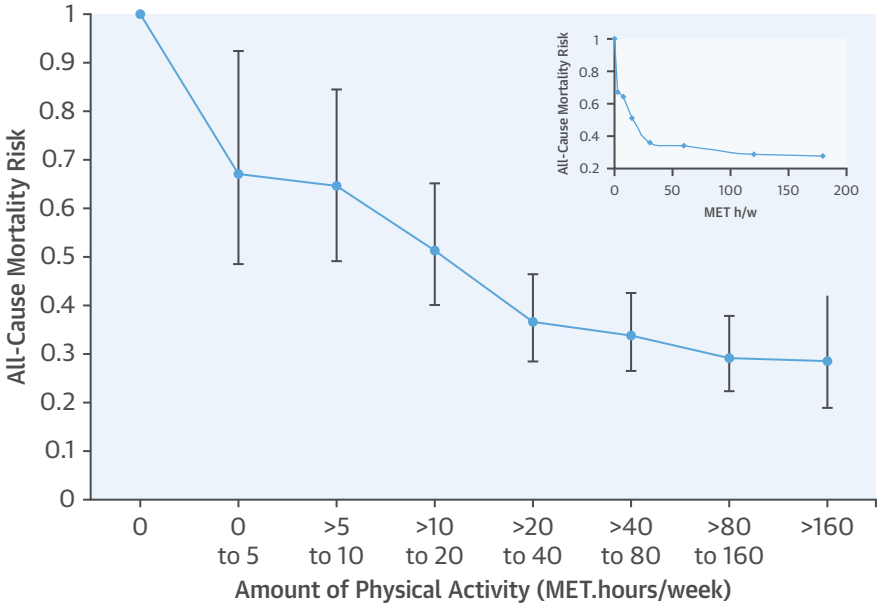
| Outcome Physical Activity | No of Patients | No of Events (%/3 yrs) | HR (95% CI) Least Active as Reference | p-value |
|---|---|---|---|---|
| **All-cause mortality** | | | | |
| Least Active | 5081 | 504 (8.65) | 1 | |
| Intermediate activity | 4857 | 313 (5.46) | 0.75 (0.65-0.87) | |
| Most Active | 4958 | 264 (4.47) | 0.70 (0.60-0.82) | <0.0001 |
| **CV death** | | | | |
| Least Active | 5081 | 307 (5.28) | 1 | |
| Intermediate activity | 4857 | 219 (3.82) | 0.89 (0.74-1.06) | |
| Most Active | 4958 | 157 (2.66) | 0.71 (0.58-0.88) | 0.0052 |
| **Non-CV death** | | | | |
| Least Active | 5081 | 154 (2.65) | 1 | |
| Intermediate activity | 4857 | 73 (1.27) | 0.54 (0.41-0.72) | |
| Most Active | 4958 | 88 (1.49) | 0.73 (0.55-0.96) | <0.0001 |
| **MACE** | | | | |
| Least Active | 5081 | 597 (10.61) | 1 | |
| Intermediate activity | 4857 | 496 (8.93) | 0.96 (0.85-1.08) | |
| Most Active | 4958 | 397 (6.92) | 0.81 (0. 71-0.92) | 0.0054 |
| **MI** | | | | |
| Least Active | 5081 | 267 (4.71) | 1 | |
| Intermediate activity | 4857 | 244 (4.36) | 1.02 (0.86-1.22) | |
| Most Active | 4958 | 211 (3.65) | 0.90 (0.74-1.08) | 0.3514 |
| **Stroke** | | | | |
| Least Active | 5081 | 98 (1.70) | 1 | |
| Intermediate activity | 4857 | 105 (1.85) | 1.15 (0.87-1.52) | |
| Most Active | 4958 | 86 (1.47) | 0.97 (0.71-1.31) | 0.4392 |



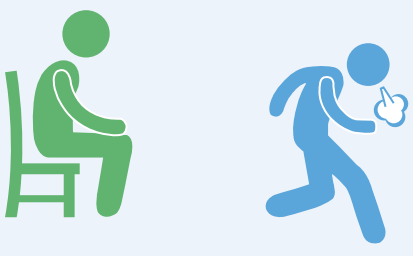

Plots are of hazard ratios (HR) and 95% confidence intervals (CI) **(A)** before and **(B)** after adjustment for covariates. Covariates included in the fully adjusted model are randomized treatment, age, body mass index, sex, systolic blood pressure, hypertension, geographic region for final reporting, prior myocardial infarction (MI), prior coronary revascularization percutaneous coronary intervention or coronary artery bypass graft, coronary heart disease, baseline diabetes, smoking, polyvascular disease, significant renal dysfunction, hemoglobin, white blood cell count, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate according to CKD-EPI (Chronic Kidney Disease-Epidemiology research group) calculator, and congestive heart failure. CV = cardiovascular; MACE = major adverse cardiac event(s).

**CENTRAL ILLUSTRATION** **Habitual Physical Activity and Mortality in Patients With Stable Coronary Artery Disease**

All-cause mortality risk associated with each doubling of habitual physical activity volume, and by linear increase in physical activity




Characteristics associated with greatest potential to benefit from increase in physical activity




↑ ABC-CHD risk score

↑ Age

Smoker

Diabetes

Peripheral artery disease

↑ Troponin T

↑ NT-proBNP

↑ LDL cholesterol

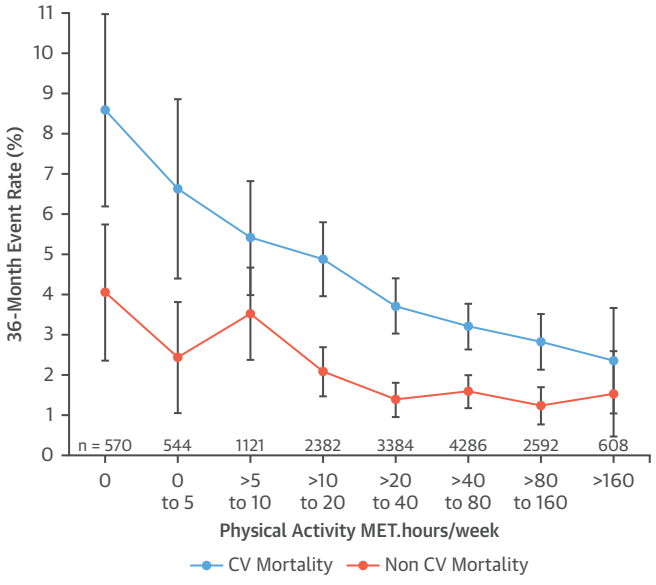
**Stewart, R.A.H. et al. J Am Coll Cardiol. 2017;70(14):1689–700.**

All-cause mortality risk associated with each doubling of habitual exercise volume and by linear increase in physical activity **(inset)** in 15,486 patients with stable coronary heart disease. Selected characteristics of patients who had the greatest reduction in mortality associated with increase in physical activity are also illustrated. ABC-CHD = Age, Biomarkers, Clinical Variables-Coronary Heart Disease; LDL = low-density lipoprotein; METs = metabolic equivalents; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Results of analyses were similar when absolute increase in METs h/week of exercise (Online Figure 1), and natural logarithm-transformed (Online Figure 2) measures of exercise were evaluated (Online Table 1).

A 1-level increase in average exercise intensity (from mild to moderate, or from moderate to vigorous) between subjects was associated with a decrease in total mortality (unadjusted HR: 0.69; 95%

**FIGURE 2 Associations Among the Volume of Mild, Moderate, and Vigorous Physical Activity and CV and Non-CV mortality**




Self-reported habitual exercise in metabolic equivalents (METs) h/week. Ten METs h/week of exercise is equivalent to 5 h of mild intensity exercise, 2.5 h of moderate intensity exercise, and 1.25 h of vigorous exercise. CV = cardiovascular.

CI: 0.64 to 0.73; adjusted HR: 0.84; 95% CI: 0.78 to 0.89), and CV mortality (unadjusted HR: 0.66; 95% CI: 0.61 to 0.71; adjusted HR: 0.81; 95% CI: 0.75 to 0.88).

Doubling the duration of exercise was also associated with lower all-cause mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.86; adjusted HR: 0.90; 95% CI: 0.87 to 0.94), and with CV mortality (unadjusted HR: 0.85; 95% CI: 0.81 to 0.89; adjusted HR: 0.93; 95% CI: 0.89 to 0.98).

Associations between the volume of exercise at the highest reported intensity and mortality are displayed in **Figure 3**. Increase in the amount of mild intensity exercise between subjects was associated with mortality in the subgroup who reported taking no moderate or vigorous exercise. In participants who reported taking no vigorous exercise, more moderate intensity exercise was also associated with lower mortality. Subjects who reported taking any vigorous exercise had lower mortality than those who took no vigorous exercise, but there was no clear association between increasing duration of vigorous exercise and either higher or lower mortality.

**SUBGROUP ANALYSIS.** Adjusted HR for all-cause mortality by increase in total physical activity are displayed for subgroups in **Figure 4**. The association between exercise volume and mortality was similar across all geographic regions. There was a larger decrease in mortality with increase in METs h/week of exercise between subjects in the least active tertile, and between subjects who reported <10 METs h/week compared with those reporting ≥10 METs h/week of moderate or vigorous exercise.

Diabetes, significant renal dysfunction, polyvascular disease, and ABC-CHD risk score above the population median were associated with a greater reduction in mortality between participants with increase in habitual physical activity (p for interaction <0.05 for all). The decrease in mortality associated with increase in exercise was also greater between patients who reported limitation of exercise by dyspnea and similar between patients who did and did not report limitation because of chest pain or discomfort.

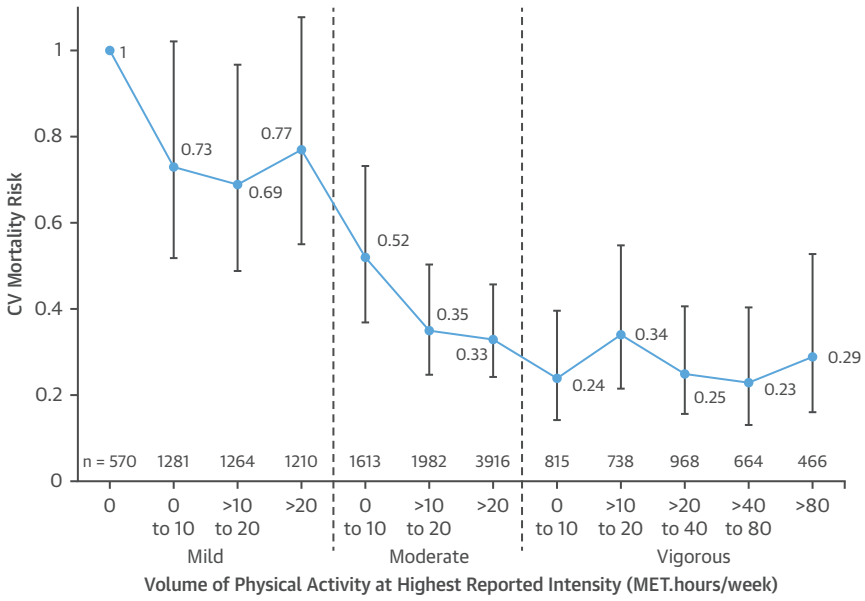
**RELATIVE IMPORTANCE OF EXERCISE AND OTHER PROGNOSTIC VARIABLES.** Of the covariates evaluated, habitual exercise was the second strongest independent predictor of mortality, after history of congestive heart failure (Online Figure 3). However, its predictive value for mortality when considered alone was modest (C-statistic = 0.586; 95% CI: 0.569 to 0.604), and it provided a modest incremental predictive improvement after considering all other covariates, (C-statistic for all covariates, excluding physical activity = 0.746; 95% CI: 0.732 to 0.761; C-statistic including physical activity = 0.750; 95% CI: 0.735 to 0.764).

## DISCUSSION

In this study of patients with stable CHD, there was a gradually lower all-cause, CV, and non-CV mortality at gradually higher self-reported habitual exercise. These associations were not linear: the difference in mortality was greater for different activities at lower levels of habitual exercise, and less pronounced for differences in activity at higher levels of exercise. This suggests important potential benefits of increasing habitual exercise in persons with stable CHD who are sedentary.

Analyses from large general population studies and others also suggest the relationship between the amount of exercise and mortality is nonlinear; greater reductions are associated with modest increases in physical activity in sedentary persons, and decrease progressively at higher levels of exercise (7–9). In a large Taiwanese population study (25), persons who exercised on average for only 15 min each day had 14% lower mortality and an increase in life expectancy of 3 years compared with persons who were completely sedentary. Mortality was lower

**FIGURE 3 Associations Between CV Mortality and the Amount of Habitual Exercise at the Highest Reported Intensity Reported by Each Participant**




The duration of mild intensity exercise each week is reported for subjects who undertake no moderate or vigorous exercise. Moderate intensity physical activity is given for patients who had no vigorous physical activity. The amount of vigorous exercise is reported for patients who reported any habitual vigorous exercise. Ten METs h/week = 5 h of mild intensity exercise, 2.5 h of moderate intensity exercise, and 1.25 h of vigorous exercise. To evaluate possible associations at high intensities of exercise, vigorous physical activity is also reported for >20 to 40 METs h (≥2.5 to 5 h), >40 to 80 METs h (>5 to 10 h), and >80 METs h (>8 h per week). Abbreviations as in Figure 2.

also in persons who exercised more, but the incremental benefit was less. In studies of runners, increase in the speed and duration of running was not associated with progressive reductions in mortality (26,27).

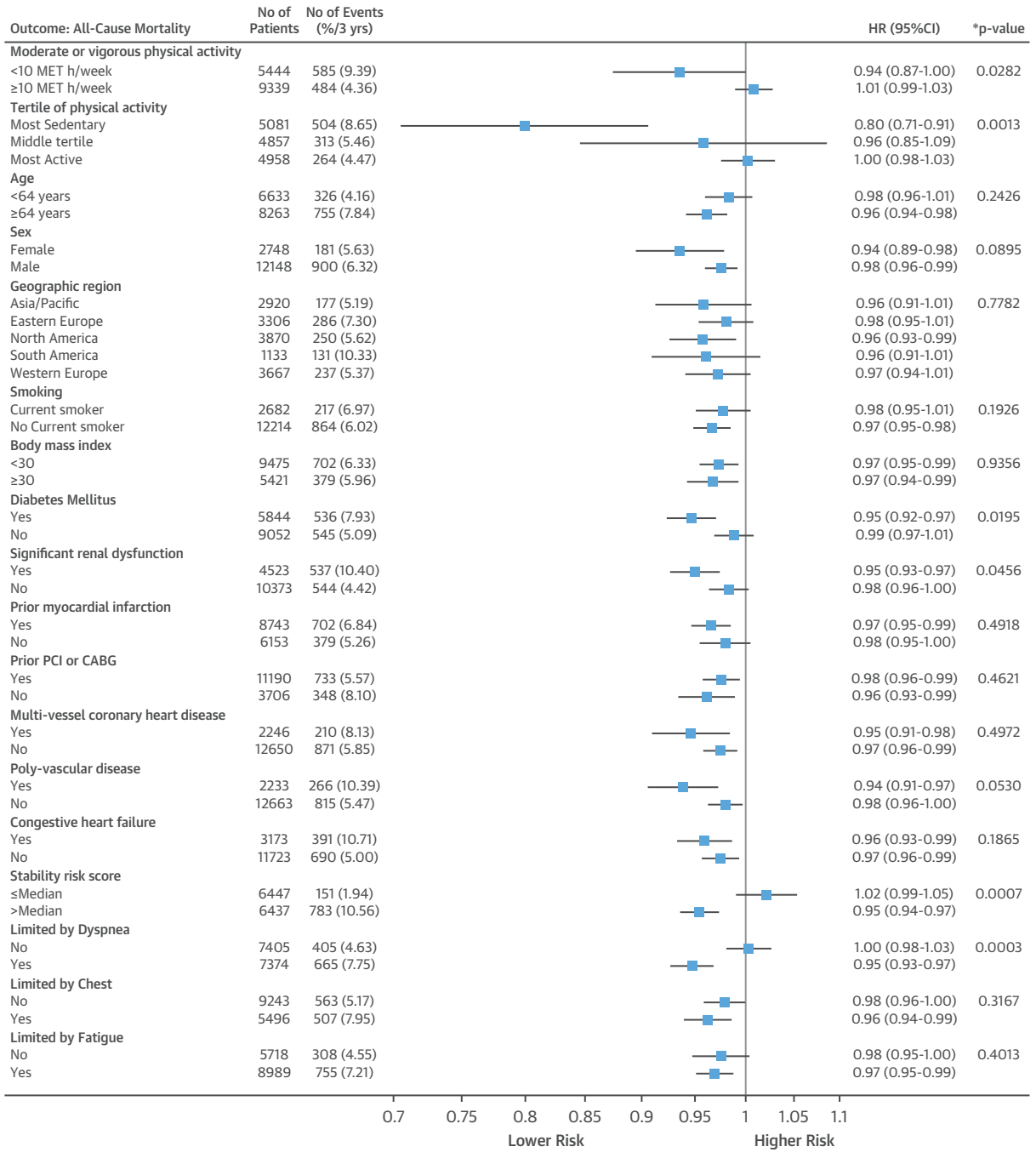
Ours is the largest analysis evaluating the dose-response relationship between habitual exercise and mortality in a global cohort of patients with stable CHD. Subgroup analyses from large cohort studies suggest associations are likely to be similar for patients with and without known CV disease, but information about the nature and severity of CV disease from these studies was limited (7–9).

Vigorous exercise may increase CV risk by triggering MI (28) or sudden death (29), and this risk could be greater in patients with stable CHD. Previous studies in both general (30) and CHD populations (12,13) suggest that mortality may be increased at very high levels of vigorous exercise. A reverse J-shaped association between exercise levels and mortality was reported in patients with stable CHD who participated in a cardiac rehabilitation program (12). In a large study of readers of a U.S. running magazine who indicated they had had a heart attack, mortality was lower for runners than for nonrunners, but mortality was higher for runners who reported ≤ compared with >7.2 METs h/day of vigorous exercise (the highest category of vigorous exercise, equivalent to running more than ~7.1 km/day) (13). However, in our study long durations of vigorous physical activity may not have been accurately quantified and the 95% CI for the risk estimates were wide, and therefore a modest increase in mortality associated with high intensities or durations of vigorous exercise cannot be excluded.

We included evaluation of mild intensity exercise, which contributed relatively more to overall physical activity in persons exercising less. For persons who undertook no moderate or vigorous exercise, mild-intensity exercise was associated with lower mortality. Reduced sedentary time and greater time spent standing are also associated with lower mortality in general population studies, especially in persons who are less active (10).

Subgroup analyses suggest the association between increased exercise and mortality is stronger in patients with the highest ABC-CHD risk score, which estimated risk from several clinical risk

**FIGURE 4 Association Between Increasing Physical Activity and Mortality in Subgroups Defined by Baseline Characteristics**




HR and 95% CI for all-cause mortality with increase in mild, moderate, and/or vigorous physical activity of 10 METs h/week, adjusted for randomized treatment, age, body mass index, sex, systolic blood pressure, hypertension, geographic region for final reporting, prior MI, prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), prior multivessel coronary heart disease, baseline diabetes, smoking, polyvascular disease, significant renal dysfunction, hemoglobin, white blood cell count, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate according to CKD-EPI (Chronic Kidney Disease-Epidemiology research group) calculator, and congestive heart failure. *The p values are for test for interaction. Abbreviations as in Figures 1 and 2.

factors and biomarkers (24). Diabetes, polyvascular disease, and limitation by dyspnea were each independently associated with a greater decrease in mortality with increase in exercise, and the association was similar for persons who did and did not report limitation of exercise by chest pain or discomfort. These observations suggest that persons with more advanced disease and/or limiting symptoms, who are often also more sedentary, could have the most to benefit from increasing habitual exercise.

**STUDY LIMITATIONS.** Causality cannot be established from observational studies. We report differences in mortality between participants who reported different levels of exercise, but randomized trials are needed to reliably determine the independent benefit from increasing habitual exercise. Socioeconomic, cultural, and societal factors were important determinants of the amount of usual physical activity (13). There were also baseline differences in risk factors, measures of disease, comorbidity, and ABC-CHD risk score by habitual physical activity. Adjustment for all covariates accounted for about one-half of the association between exercise and mortality. On the other hand, because exercise has favorable effects on multiple CV risks factors, adjustment for all covariates may also underestimate potential benefits from increasing exercise. General population studies, where pre-existing disease is less likely to confound evaluations, have reported a similar dose-response relationship with long-term mortality (8,25).

Assessment of usual exercise was based on a simple self-reported questionnaire, which is easier to administer than formal exercise testing during routine medical consultation and can also be used to guide recommendations based on reported levels of exercise. However, questionnaires are subjective; patients may overestimate habitual exercise, and estimates of physical activity volume are likely to be imprecise. These limitations would be expected to result in an underestimate of the true strength of association between exercise and mortality.

The study evaluated high-risk clinical trial participants who may have different characteristics than do other patients with stable CHD. However, associations between self-reported exercise and mortality were consistent across diverse geographic regions and by various demographic variables, suggesting results are probably broadly representative.

Different approaches were explored to describe the nonlinear association between habitual exercise and outcomes. Doubling of exercise volume, which can be achieved by increasing average exercise intensity by 1 level, doubling the duration of exercise, or a combination of both were chosen because it is relatively easy for patients and clinicians to understand. However, associations were strongly statistically significant for all measures used to describe increase in exercise volume, as reported in the Online Appendix.

## CONCLUSIONS

For sedentary persons, smaller amounts of habitual mild or moderate intensity exercise may have substantial health benefits, whereas persons who already undertake regular moderate or vigorous intensity physical activity may benefit less from increasing exercise. At a population level, the greatest benefits to health are likely to be achieved by modest increases in exercise in sedentary persons, especially in persons who have a higher risk of adverse events, and those with exertional angina and dyspnea. However, because low physical activity may reflect poorer health, randomized clinical trials are still needed to confirm that increasing physical activity also reduces mortality.

**ACKNOWLEDGMENTS** The authors thank all patients who participated in the STABILITY trial, as well as study nurses and investigators at 639 participating sites.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** In patients with stable ischemic heart disease, a modest increase in exercise is associated with reduced CV and all-cause mortality, particularly in sedentary individuals and those at highest CV risk. There is no evidence of either harm or benefit from increasing the duration of vigorous activity or harm from more exercise in patients limited by angina or dyspnea.

**TRANSLATIONAL OUTLOOK:** There is a need for simple strategies that encourage regular exercise in sedentary patients with stable coronary disease and for randomized trials to confirm that increasing exercise and reduced mortality are causally related.

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**KEY WORDS** cardiac rehabilitation, coronary artery disease, exercise, physical activity

**APPENDIX** For supplemental figures and a table, please see the online version of this article.