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Systematic Review of Physical Activity Trajectories and Mortality in Patients With Coronary Artery Disease

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ABSTRACT

BACKGROUND The role of lifestyle physical activity (PA) trajectories in the mortality risk of patients with coronary heart disease (CHD) remains unclear.

OBJECTIVES The purpose of this study was to determine the association of longitudinal PA trajectories with all-cause and cardiovascular disease (CVD) mortality in patients with CHD.

METHODS Longitudinal cohorts reporting the association of PA trajectories with mortality in patients with CHD were identified in April 2021 by searching 5 databases without language restrictions. Published HRs and 95% CIs were pooled using random effects models and bias assessed by Egger regression.

RESULTS A total of 9 prospective cohorts included 33,576 patients. The mean age was 62.5 years. The maximum follow-up was 15.7 years. All of the studies assessed PA through validated questionnaires, and mortality was well documented. Changes in PA defined 4 nominal PA trajectories. Compared with always-inactive patients, the risk of all-cause mortality was 50% lower in those who remained active (HR: 0.50; 95% CI: 0.39-0.63); 45% lower in those who were inactive but became active (HR: 0.55; 95% CI: 0.44-0.7); and 20% lower in those who were active but became inactive (HR: 0.80; 95% CI: 0.64-0.99). Similar results were observed for CVD mortality, except for the category of decreased activity (HR: 0.91; 95% CI: 0.67-1.24). The overall risk of bias was low. No evidence of publication bias was found. Multiple sensitivity analyses provided consistent results.

CONCLUSIONS This study illustrates how patients with CHD may benefit by preserving or adopting an active lifestyle. The observation that the benefits of past activity can be weakened or lost if PA is not maintained may be confounded by disease progression. (J Am Coll Cardiol 2022;79:1690–1700) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Patients with coronary heart disease (CHD) have an increased risk of both all-cause and cardiovascular disease mortality.[1] Regular physical activity (PA) is a major modifiable protective factor against cardiovascular disease and death.[2] Several mechanisms may be responsible for the benefits associated with PA in CHD patients, including endothelial function improvement,[3,4] anti-atherosclerotic,[4,5] and anti-inflammatory[6] effects. American and European guidelines thus recommend that adults with chronic health conditions engage in regular lifestyle PA, according to their abilities, and

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avoid inactivity. However, the current recommendations are largely based on longitudinal studies that use either a single assessment or an average of PA levels assessed over time.[7-9] The exact role of lifestyle PA trajectories in the mortality risk of patients with CHD remains unclear.

Previous observational studies have consistently reported a lower risk of mortality in CHD patients who remain physically active compared with those who remain sedentary.[10,11] However, the evidence is inconclusive in those who change their PA patterns over time. Some studies have reported no impact of PA trajectories on mortality risk,[11-14] whereas others have reported increased[14] or decreased[15,16] mortality risk in CHD patients who reduced their PA levels, and still others have reported a decreased mortality risk in those who increased their PA levels.[12,13,15,17,18] Previous meta-analyses of clinical trials investigating the impact of PA in CHD patients have mainly focused on cardiac rehabilitation[19] rather than lifestyle PA. Despite the effectiveness of cardiac rehabilitation,[20] several barriers, including low referrals, low uptake, and poor adherence, frequently prevent its widespread use. Moreover, randomized clinical trials are limited in follow-up, and usually have an underrepresentation of women,[21,22] frail, and older adults.[23] To date there has been no synthesis of literature on the impact that lifestyle PA trajectories have on CHD patients. A thorough evaluation of the current evidence could be crucial to eventually informing prevention guidelines for patients with CHD. We performed a systematic review and meta-analysis of the association of longitudinal trajectories of PA with all-cause and cardiovascular disease (CVD) mortality in patients with CHD.

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METHODS

We followed the Cochrane Handbook of Systematic Reviews of Intervention, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement,[24] the Scientific Statement from the American Heart Association on systematic review and meta-analysis of cardiac prevention and treatment studies,[25] and the Meta-analysis of Observational Studies in Epidemiology framework.[26] We searched for prospective and retrospective cohort studies that analyzed the associations of PA trajectories in CHD patients with all-cause and/or CVD mortality (PROSPERO CRD42019130956). We selected the studies that met the following criteria: 1) had a longitudinal observational design; 2) were conducted in adult (age ≥18 years) patients with CHD; 3) reported the associations of at least 2-point PA trajectories with all-cause and/or CVD mortality; and 4) reported the results using any measure of relative risk. We excluded papers with incomplete information, systematic reviews and meta-analyses, and reports from meetings or congresses. The details for the search strategy, study selection, and data extraction methods are available in the Supplemental Methods (Supplemental Section 1).

ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease
CVD = cardiovascular disease
HF = heart failure
PA = physical activity
PAD = peripheral artery disease

DATA SYNTHESIS. We conducted a narrative synthesis of the findings from the included studies. We used published aggregated data from each study and applied the inverse variance weighted method to combine[27] the extracted HRs and their 95% CIs using random-effects models to account for the effect of between-study heterogeneity.[28] We quantified statistical heterogeneity using the I^2 statistic. Heterogeneity was classified according to the most recent version of the Cochrane Handbook: 0%-40%: might not be important; 30%-60%: may represent moderate heterogeneity; 50%-90%: may represent substantial heterogeneity; 75%-100%: considerable heterogeneity.[29] We evaluated the publication bias and small-study effects by means of funnel plots and Egger regression symmetry tests.[30] Statistical analyses were performed in StataIC 16 (Stata Corp).

SENSITIVITY ANALYSES. We did the following sensitivity analyses:

1. To assess the impact of individual studies on the overall results, we calculated the pooled risk estimates and heterogeneity after removing the studies 1 by 1 from the analyses.
2. To account for a possible influence of the source population on our results, we stratified the studies based on the type of CHD (chronic CHD vs acute CHD) and the origin of recruitment of CHD patients (general population cohorts vs CHD cohorts).
3. We performed random-effects meta-regression analyses to identify sources of between-study heterogeneity. We considered source populations, time between follow-up, proportion of patients in each trajectory, type of CHD, mean age, and sex as independent variables and risk estimates as the dependent variable. We conducted stratified analysis according to the type of CHD, the source population of the cohort, and by the extracted mean age of the cohorts (age 65 years).
4. To account for Secular trends, we performed 2 cumulative meta-analyses for each outcome according to year of publication and time of follow-up.

TABLE 1 General Characteristics of the Included Studies

First Author	Country, Year	First Year of Recruitment	Total Participants	All-Cause Mortality	CVD Mortality	Cohort Selection	CHD Type	Female %	Mean Age, y	Comorbidities DM, HTA, %	Adjustment for
Steffen-Batey et al[16]	United States, 2000	1988	406	106	—	Survivors beyond 30 days of a first MI (CHD- exclusive cohort)	Acute	37	59	33, 55.6	Age at first MI, severity of MI, sex, ethnicity, smoking, DM, HTA, hypercholesterolemia
Wannamethee et al[14]	United Kingdom, 2000	1978	772	131	94	Men with established CHD (general population cohort)	Chronic	0	63	NR	Age, smoking, social class, obesity, DM, stroke
Gerber et al[18]	Israel, 2011	1992	1,521	388	-	Patients with incident MI (CHD-exclusive cohort)	Acute	18	53	24.3, 37.2	Age, sex, HTA, DM, dyslipidemia, smoking, obesity, comorbidity index, socioeconomic status, HF
Gorczyca et al[12]	United States, 2017	1993	856	275	120	Postmenopausal women in the Women's Health Initiative Observational Study who experienced MI (general population cohort)	Acute	100	67	13.4, 51.7	Age, education, race, income, depression, history of MI, smoking, alcohol consumption
Ekblom et al[15]	Sweden, 2018	2004	22,227	1,087	—	Patients who were diagnosed with their first MI (CHD-exclusive cohort)	Acute	26	62	NR	Age, sex, BMI, GFR, LVEF, STEMI, smoking, medication, PCI, participation in CR, QOL
Lahtinen et al[10]	Finland, 2018	2007	1,746	147	68	Patients with angiographically documented stable CHD (CHD-exclusive cohort)	Chronic	32	67	42, NR	Age, sex, BMI, DM, LVEF, smoking, alcohol consumption, history of MI
Moholdt et al[11]	Norway, 2018	1985	3,307	1,493	819	Patients with CHD from the HUNT Nord Trøndelag Health Study (general population cohort)	Chronic	37	69	10.5, 79.5	Age, sex, DM, HTA, smoking, alcohol consumption, BMI
Mok et al[13,a]	United Kingdom, 2019	1993	1,090	518	239	Patients with CHD from the EPIC-Norfolk study (general population cohort)	Chronic	56	58	NR	Age, sex, smoking, social class, alcohol intake, diet quality, COPD, cancer, stroke
Al-Shaar et al[17]	United States, 2020	1988	1,651			Survivors beyond 2 years of a first MI (general population cohort).	Chronic	0	65	13.9, 55	Age, race, marital status, smoking, year of MI diagnosis, alcohol consumption, incidence of cancer during follow-up, stroke

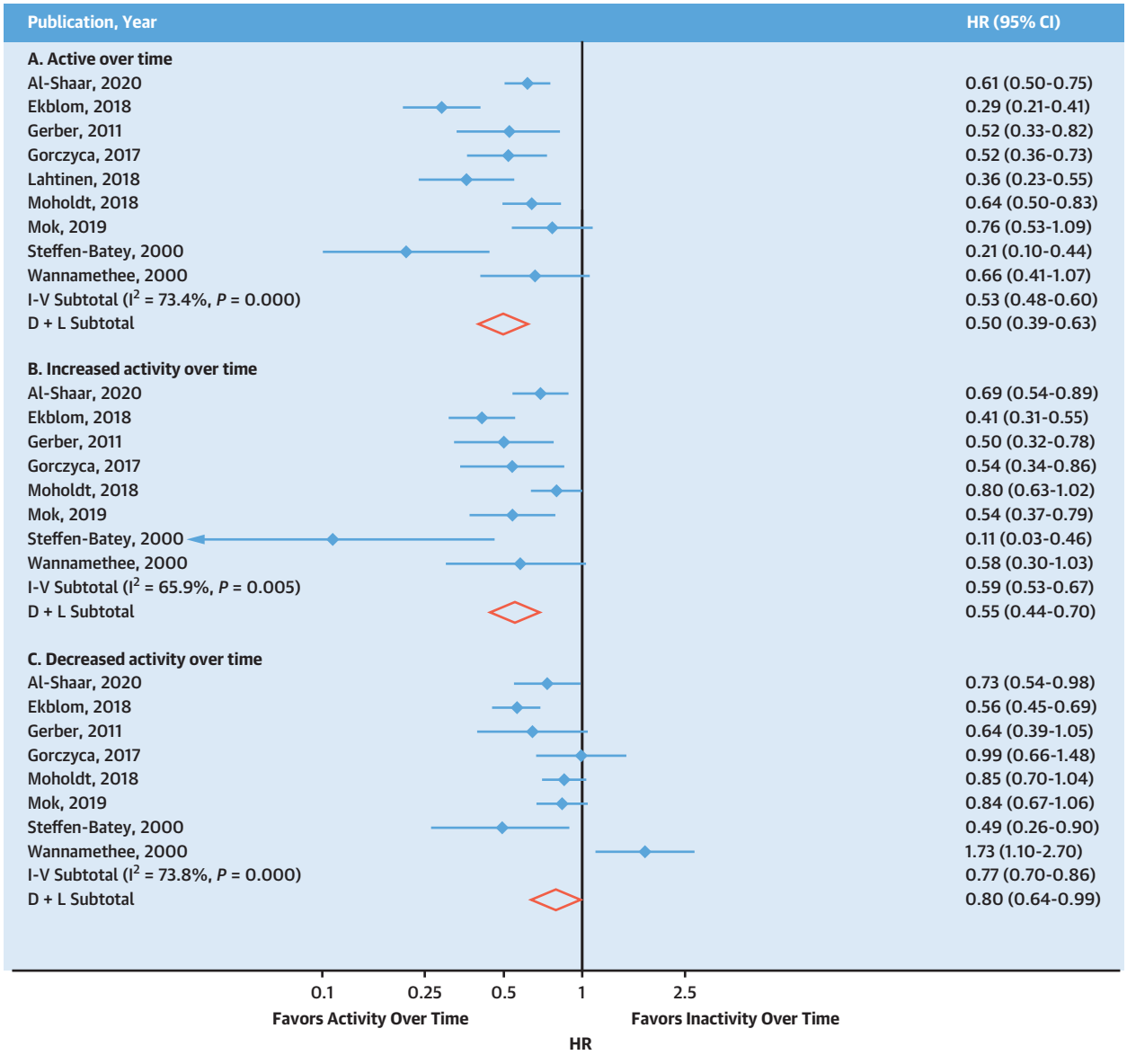
[a]Data for HRs provided by authors upon request for the present meta-analysis; data on comorbidities not reported specifically for the CHD population.

BMI = body mass index; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CR = cardiac rehabilitation; CVD = cardiovascular disease; DM = diabetes mellitus; GFR = glomerular filtration rate; HF = heart failure; HTA = hypertension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; QOL = quality of life.

5. Because patients with severe disease may be more prone to sedentary behavior, we restricted the analyses to studies accounting for reverse causation.
6. To account for a possible influence of the quality of the studies in the results, we restricted the analyses to studies with low risk of bias.
7. To account for unmeasured confounding bias, we quantified for each pooled result the magnitude of unmeasured confounding (E values) capable of reducing the HRs to the null[31,32] (Supplemental Appendix Section 1).

We restricted the analysis to: 1) studies that evaluated changes in PA patterns before and after diagnosis of CHD; 2) studies in which PA trajectory was established during follow-up; 3) studies in which PA trajectory was established before follow-up; and 4) studies that used time-updated methods in the survival analysis. If both prospective and retrospective studies were included, we would perform stratified analyses according to these types of studies to account for potential differences in results across designs.

FIGURE 1 Meta-Analysis on the Associations of PA Trajectories With All-Cause Mortality

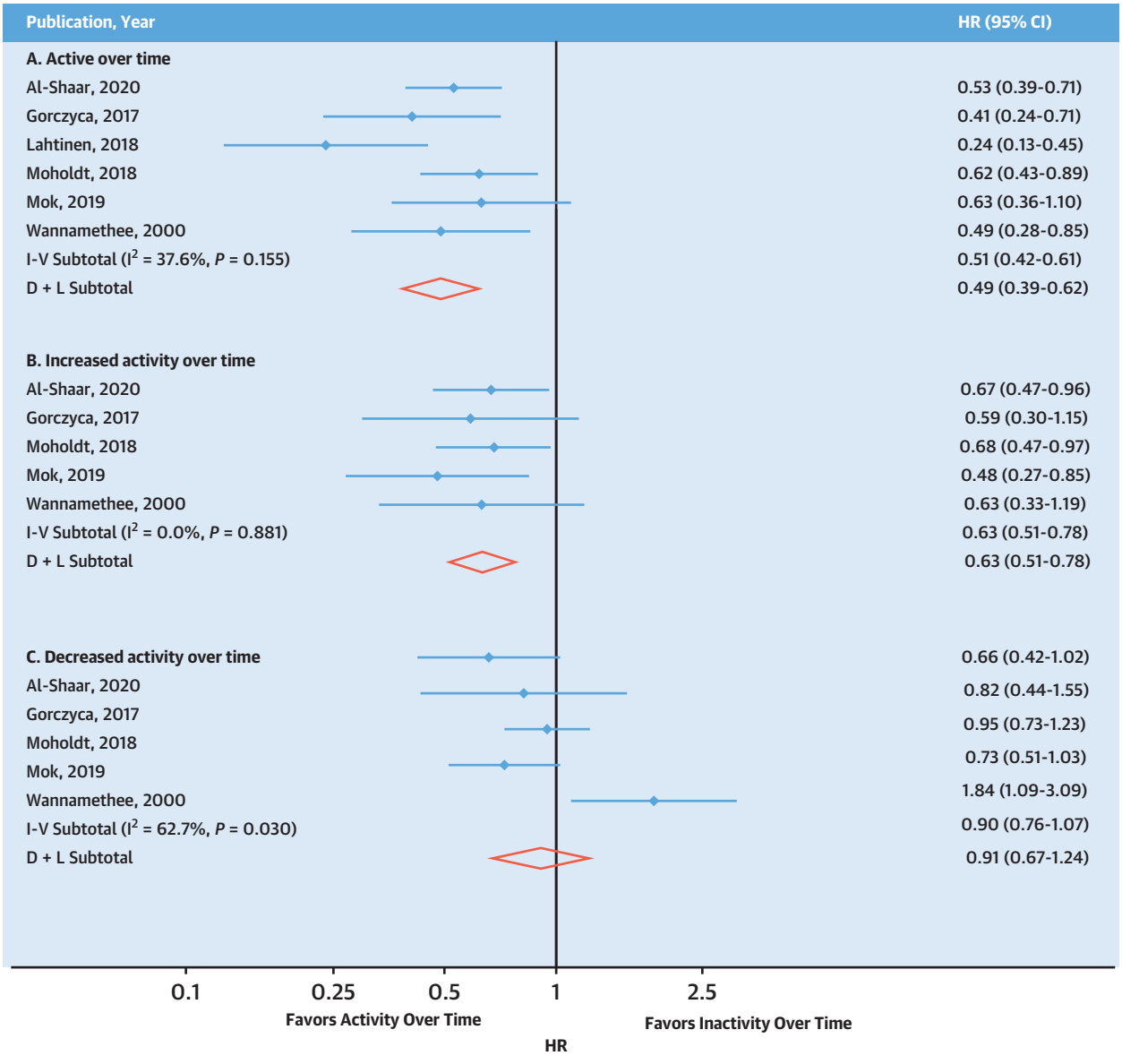


Forest plot summarizing the pooled HRs for each PA trajectory and all-cause mortality. For each study, **blue diamonds** and **horizontal lines** correspond to the respective point estimate and accompanying 95% CI. All the estimates are compared with inactive over time as the reference category. The **vertical solid line** on the forest plot represents the point estimate of HR: 1. The **red diamonds** represent the 95% CI of the summary pooled estimate of the effect and are centered on pooled HRs. Heterogeneity estimate of I^2 accompanies the summary estimate. PA = physical activity.

RESULTS

IDENTIFICATION OF RELEVANT STUDIES. After deduplication, we identified 12,250 potentially relevant citations. After initial screening based on the title and abstracts, the full texts of 42 papers were selected for detailed evaluation. After full-text assessment, we excluded 33 papers because their analyses did not include trajectories of PA (Supplemental Figure 1). The remaining 9 papers evaluated longitudinal associations of PA with the outcomes of interest and were included in the systematic review and meta-analysis.[10-18] All of the included studies were prospective, analyzed

FIGURE 2 **Meta-Analysis on the Associations of PA Trajectories With CVD Mortality**

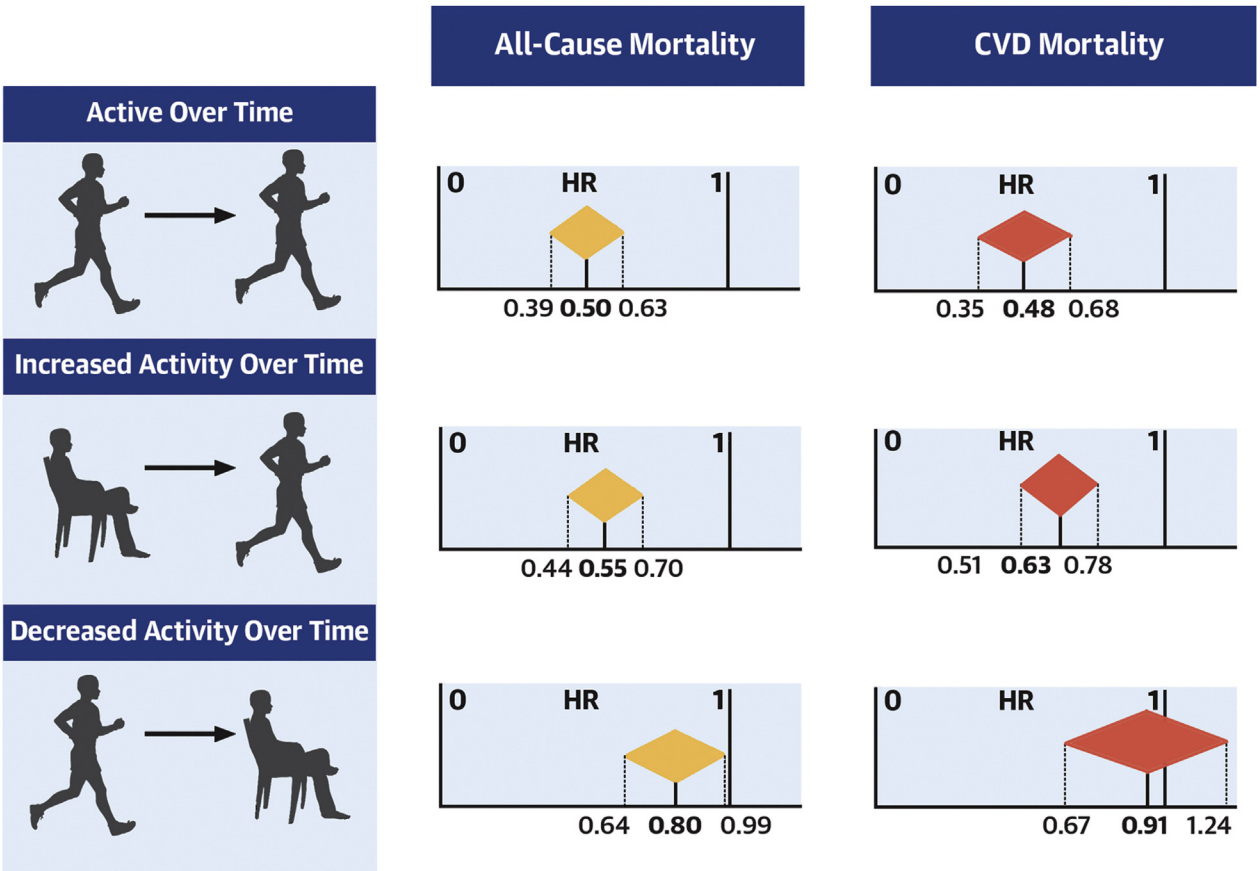


Forest plot summarizing the pooled HRs for each PA trajectory and CVD mortality. For each study, **blue diamonds** and **horizontal lines** correspond to the respective point estimate and accompanying 95% CI. All the estimates are compared with inactive over time as the reference category. The **vertical solid line** on the forest plot represents the point estimate of HR: 1. The **red diamonds** represent the 95% CI of the summary pooled estimate of the effect and are centered on pooled HRs. Heterogeneity estimate of I^2 accompanies the summary estimate. CVD = cardiovascular disease; PA = physical activity.

mortality as their main outcome, and reported their results as HRs. All the studies analyzed all-cause mortality, and 6 studies additionally reported CVD mortality.[10-14,17]

GENERAL CHARACTERISTICS OF THE INCLUDED STUDIES. Detailed characteristics of the included studies are provided in Table 1. Overall, these studies included 33,576 patients, and the sample size of the individual studies ranged from 406 to 22,227. The mean age, calculated as the weighted average of the exported mean ages from each study, was 62.5 years. The proportion of women ranged from 18% to 56% among studies including patients from both sexes.[10,11,13,15,16,18] One study included only women,[12]

CENTRAL ILLUSTRATION **Associations of Physical Activity Trajectories With All-Cause and CVD Mortality**



Gonzalez-Jaramillo N, et al. J Am Coll Cardiol. 2022;79(17):1690–1700.

This meta-analysis evaluating trajectories of lifestyle physical activity in 33,576 patients with coronary heart disease illustrate how patients with coronary heart disease may benefit by preserving or adopting—even if they previously were inactive—an active lifestyle. Compared with being inactive over time, continuing an active lifestyle is associated with the highest survival. However, patients with coronary heart disease can overcome prior inactivity by becoming active later in life. **Diamonds** represent the 95% CI of the summary pooled estimate of the effect and are centered on pooled HRs. All estimates are compared with inactive over time as the reference category. CVD = cardiovascular disease.

and 2 studies were performed in men exclusively.[14,17] In total, 5 of the 9 studies were performed in patients with chronic CHD[10,11,13,17]; the remaining 4 studies recruited patients after an acute coronary event.[12,15,16,18] The studies adjusted for multiple potential confounders, including age, sex, ethnicity, smoking, diabetes, hypertension, left ventricular ejection fraction, glomerular filtration rate, socioeconomic status, and body mass index, among others (**Table 1**). None of the studies included patients with peripheral artery disease or heart failure at baseline.

MEASUREMENT OF THE EXPOSURE. All studies assessed PA through validated questionnaires (Supplemental Table 1). Of the 9 studies, 8 evaluated changes in PA patterns before and after diagnosis of CHD,[10-14,16-18] and 1 evaluated changes in PA patterns at different times after diagnosis of CHD.[15] Despite the variations in the guidelines across time concerning recommendations of PA, in general, the cutoff points of activity and inactivity for the majority of the studies[11-14,17,18] were in agreement with current PA guidelines.[7] All of the studies calculated PA trajectories based on the comparison of activity status at baseline and follow-up and reported 4 longitudinal nominal categories: inactive over time, active over time, increased activity over time, and decreased activity over time. All of the studies defined increased activity over time as moving from the inactive to the

active category and decreased activity over time as moving from the active to the inactive category. In total, 8 of the 9 studies regarded being inactive as the reference category.[11-18] The remaining study[10] defined the reference category as being consistently active. We converted that study's reference category to "inactive over time" by using the multiplicative inverse of the reported HR. Supplemental Table 1 provides a description of the measurements and definitions of PA trajectories across studies.

MEASUREMENT OF THE OUTCOMES. In total, 7 of 9 studies reported their time zero for follow-up (Supplemental Table 1).[10,13-18] Three studies started the follow-up after the second PA assessment, meaning that the trajectories were established before starting the follow-up.[10,13,14] Four studies considered the baseline as the time zero for follow-up, meaning that the trajectories were established during the follow-up.[15-18] Five studies used time-updated methods in the survival analysis (Supplemental Table 1).[11-13,15,18] Follow-up duration ranged from 4.2 to 15.7 years (Supplemental Table 1). The all-cause mortality rate was 14.3% (4,813 of 33,576), and the CVD mortality rate was 8.6% (819 of 9,422). All of the studies had well-documented mortality assessments.

POTENTIAL BIAS AND QUALITY ASSESSMENT. The funnel plots for the association of PA trajectories with all-cause and CVD mortality are available in Supplemental Figure 2. The Egger tests did not indicate asymmetry or small-study effects (*P* values = 0.19 and 0.26, respectively), and thus provided no evidence of publication bias. The quality assessment results are provided in the Supplemental Section 2. Initial agreement on study quality between the 2 raters was 85%, and full consensus was reached after discussion. The study quality scores ranged from 7 of 9 to 9 of 9. In total, 7 of the 9 studies had low risk of bias[10-13,15,16,18] and 2 studies had moderate risk of bias (Supplemental Table 2).[14,17] Two studies[14,17] were conducted in very-selected populations, which reduced the quality in the selection domain. All of the studies used a self-assessment of the exposure, which also reduced the quality in the selection domain, except for 1 study that used a self-assessment tool that was validated by using individually calibrated combined movement and heart rate monitoring.[13] All of the studies analyzing PA trajectories in patients with acute CHD had low risk of bias. In total, 3 of 5 studies analyzing PA trajectories in patients with chronic CHD had low risk of bias. Traffic light plots for all-cause mortality in the acute and chronic CHD settings separately and for CVD mortality are provided in Supplemental Figure 3.

PHYSICAL ACTIVITY TRAJECTORIES AND ALL-CAUSE MORTALITY. All of the studies assessed the association between longitudinal changes of PA and all-cause mortality. Compared with those who remained inactive, the risk of all-cause mortality was 50% lower for patients who remained active (HR: 0.50; 95% CI: 0.39-0.63), 45% lower for those who increased their PA levels (HR: 0.55; 95% CI: 0.44-0.70), and 20% lower for those who decreased their PA levels (HR: 0.80; 95% CI: 0.64-0.99). The heterogeneity (I^2) ranged from 65.9% to 73.8% (**Figure 1**). Source population of the cohorts explained part of the heterogeneity (Supplemental Table 3). Hence, when we restricted the analysis to cohorts enrolling only CHD patients, the heterogeneity ranged from 0% to 53.6% (Supplemental Figure 4c). The heterogeneity ranged from 0% to 63% when we restricted the analysis to studies that included CHD patients from general population cohorts (Supplemental Figure 4d).

ACUTE CHD VS CHRONIC CHD. Four cohorts included 25,010 patients with acute CHD.[12,15,16,18] Compared with those who remained inactive over time, the risk of all-cause mortality was 62% lower in the active over time category (HR: 0.38; 95% CI: 0.25-0.56), 56% lower for those who increased PA levels (HR: 0.44; 95% CI: 0.32-0.60), and 35% lower for those with decreased activity (HR: 0.65; 95% CI: 0.48-0.88) (Supplemental Figure 4a). The heterogeneity (I^2) ranged from 43% to 69.3%.

Five cohorts included 8566 patients with chronic CHD.[10,11,13,17] Compared with those who remained inactive, patients who remained active had a 40% lower mortality risk (HR: 0.6; 95% CI: 0.5-0.73), those whose activity increased had a 31% lower mortality risk (HR: 0.69; 95% CI: 0.59-0.82), and those with decreased activity over time had no difference in mortality risk (HR: 0.92; 95% CI: 0.71-1.19) (Supplemental Figure 4b). The heterogeneity (I^2) ranged from 10.3% to 71.4%.

COMPARISON ACCORDING TO THE SOURCE POPULATION OF THE COHORTS. Five cohorts included 25,900 patients with CHD selected from CHD-exclusive cohorts. Compared with patients remaining inactive, those who remained active had a 66% lower mortality risk (HR: 0.34; 95% CI: 0.25-0.47), those whose activity increased had a 61% lower mortality risk (HR: 0.39; 95% CI: 0.25-0.61), and those with decreased activity over time had a 54% lower mortality risk (HR: 0.56; 95% CI: 0.47-0.68) (Supplemental Figure 4c).

In total, 4 cohorts included 7,676 patients with CHD selected from general population cohorts. Compared with those who remained inactive, patients who

remained active had a 37% lower mortality risk (HR: 0.63; 95% CI: 0.55-0.71), those whose activity increased had a 33% lower mortality risk (HR: 0.67; 95% CI: 0.598-0.79), and those with decreased activity over time had no difference in mortality risk (HR: 0.93; 95% CI: 0.75-1.15) (Supplemental Figure 4d).

PHYSICAL ACTIVITY TRAJECTORIES AND CARDIOVASCULAR MORTALITY. A total of 6 studies including 9,422 patients investigated the association of PA trajectories with cardiovascular mortality (**Figure 2**).[10-14,17] The heterogeneity (I^2) ranged from 0% to 62.7%. Compared with those who remained inactive, the risk for CVD mortality was 51% lower among those who remained active (HR: 0.49; 95% CI: 0.39-0.62), was 27% lower for those whose activity increased (HR: 0.63; 95% CI: 0.51-0.78), and was not statistically different for those whose activity decreased over time (HR: 0.91; 95% CI: 0.67-1.24). In total, 5 of the 6 studies were performed in chronic CHD cohorts,[10,11,13,14,17] and 1 study was performed in post-MI patients.[12] After restricting the analyses to the chronic CHD cohorts, we obtained consistent findings (Supplemental Figure 4e). The results also remained consistent after restricting the analysis to the cohorts that selected CHD patients from the general population[12-14,17] (Supplemental Figure 4f).

SENSITIVITY ANALYSES. Results remained consistent after exclusion of any single study at a time from the meta-analyses of all-cause and CVD mortality (Supplemental Figure 5). Source of the CHD populations, time between follow-up, and type of CHD were identified as important sources of heterogeneity in the meta-regression, but not sex, proportion of patients in each category of trajectory, or age (Supplemental Table 3). Results remained consistent after performing separate analysis according to mean age of the cohorts below and above 65 years (Supplemental Figure 6). Cumulative meta-analyses according to the year of publication (Supplemental Figures 7 and 8) and length of follow-up did not provide evidence of secular trends for either all-cause or CVD mortality (Supplemental Figures 9 and 10). Results remained consistent after restricting the analyses to studies accounting for reverse causation (Supplemental Figure 11) and low risk of bias (Supplemental Figure 12). Results also remained consistent after restricting the analysis to the studies that evaluated changes in PA patterns before and after CHD onset (Supplemental Figure 13) and after restricting the analysis to the studies according to the time when the trajectories were established in relation to the follow-up (Supplemental Figures 14 and 15), and the use of time-updated methods in the survival analysis (Supplemental Figure 16). All of the results from the sensitivity analyses are available in Supplemental Section 4.

DISCUSSION

MAIN FINDINGS. In this systematic review and meta-analysis of 9 longitudinal cohorts involving 33,576 patients with CHD, we evaluated the risk of all-cause and CVD mortality across 4 PA trajectories: inactive over time, active over time, increased activity over time, and decreased activity over time. Compared with patients who were inactive over time, the risk of all-cause mortality was 50% lower in those who were active over time, 45% lower in those who were inactive but became active, and 20% lower in those who had been active but became inactive (**Central Illustration**). Similar results were observed for CVD mortality in those who remained active or became active. However, CVD mortality was not statistically different for those whose activity decreased over time, compared with those who remained inactive.

This may indicate that active patients should be encouraged to preserve active lifestyles after CHD. These results also imply that irrespective of previous PA levels, it is particularly important how patients change their PA over time following a diagnosis of CHD. Patients with established CHD can overcome prior years of inactivity and obtain survival benefits similar to those who remained active. However, the benefits of PA can be attenuated or even lost if the activity is not maintained. As shown by our sensitivity analyses, our results are applicable for patients in both acute and chronic CHD settings, patients who change their PA patterns before and after the onset of CHD, and those who only change their PA patterns following the onset of CHD.

The associations of PA trajectories with mortality can be influenced by sociodemographic and cardiovascular risk factors and treatments.[33] Individuals with chronic conditions and more severe diseases can decrease PA over time and adopt a sedentary behavior. Traditional risk factors for CHD, such as diabetes, hypertension, smoking, and hypercholesterolemia, are associated with endothelial dysfunction, which in turn results in impaired nitric oxide production, abnormal vasoconstriction, chronic inflammation, and increased oxidative stress.[34] Endothelial dysfunction, inflammation,[35] and oxidative stress[36] play an important role in both the pathogenesis and prognosis of CHD. Comorbidities can thus contribute to explain the higher mortality risk in patients who decrease PA over time, compared with those who remained or became active during the

follow-up. Nevertheless, we based the results of our meta-analysis on independent estimates adjusted for multiple covariates, including age, sex, ethnicity, socioeconomic status, education, smoking, obesity, dyslipidemia, diabetes, chronic obstructive pulmonary disease, medications, and cardiac rehabilitation. Moreover, the associations of PA trajectories and mortality also remained consistent after restricting the analyses to studies controlling for reverse causation.[12,15,16]

However, the potential role of unmeasured confounding in the results of the decreasing-activity category cannot be excluded given the observational design of our meta-analysis. For instance, the E-value for the association of decreased activity with all-cause mortality was 1.81, meaning that residual confounding could explain the observed association if there exists an unmeasured confounder associated with decreased PA and mortality with an HR of at least 1.81. Heart failure (HF) and peripheral artery disease (PAD) have been associated with a doubled risk of inactivity and mortality in patients with CHD.[37,38] In our meta-analysis, only 1 study adjusted for incident HF during the follow-up, and none of the studies adjusted for PAD. Therefore, it is likely that an unmeasured confounder that appeared during the follow-up, such as PAD or HF, would affect the association of decreasing PA over time and all-cause mortality. However, HF and PAD would not explain away the results for the other 2 remaining categories where the E values were higher than 2.6. Furthermore, it is unlikely that patients with PAD or HF increase their PA or remain as active as before having a myocardial infarction. Further research may help to clarify the potential confounding or mediating role of HF and PAD on the established association of mortality in patients with CHD that follow a trajectory of decreased activity.

STUDY STRENGTHS. To our knowledge, this is the first systematic review and meta-analysis to summarize the evidence and gather such a large body of data on the longitudinal associations of PA trajectories with all-cause and CVD mortality in patients with CHD. All of the eligible studies were published after 2000, and more than one-half of them were published in the past 2 years, which demonstrates the recent and growing interest in the field of PA trajectories. The 9 studies we included performed multiple assessments of PA levels over time. We used strict criteria to assess the quality of these studies, and the risk of bias of the individual studies was low to moderate. We performed multiple sensitivity analyses, which provided consistent findings and identified potential sources of heterogeneity. The magnitude of the associations also remained consistent irrespective of the length of follow-up, which ranged from 4.2 to 14.7 years. Although 1 study[15] contributed nearly two-thirds of the combined sample, no single study dominated the results, and no evidence of publication bias was found.

IMPORTANCE OF FINDINGS. Based on a broad base of evidence from different countries, this meta-analysis provides new insights on PA trajectories that imply benefits from adopting a more active lifestyle and the possible harms of adopting a less active lifestyle among CHD patients. Beyond the results from clinical trials performed in cardiac rehabilitation settings, we provided long-term real-world evidence showing that the survival benefits of lifestyle PA for CHD patients are likely not solely dependent on past levels of activity, but are combined with present levels of PA as well. Our results have important implications for clinical practice. The evaluation of habitual PA and the analysis of individual trajectories should become part of the routine work-up of CHD patients. Incorporating CHD patients' PA trajectories evaluation into the clinical routine could guide prognosis, counseling, and shared-decision-making, and could trigger a deeper analysis of comorbidities and functional status in case of decreasing activity.

STUDY LIMITATIONS. First, all of the individual studies relied on self-reports of PA.[39] However, all of them used validated questionnaires, which are deemed appropriate to address changes in PA over time.[40] Another limitation is that we could not isolate the role of potential confounders such as comorbidities, smoking, frailty, and diet. Given that we did not analyze individual patients' data, the meta-regression for sex and age should be interpreted cautiously. The use of categories of activity facilitates interpretability but leads to a loss of information. For instance, the grouping of PA data into 4 trajectories allowed us to neither evaluate a dose-response gradient nor analyze if small changes in PA levels may affect the prognosis. The point estimates for the main analysis were heterogeneous. Nonetheless, we identified potential sources of heterogeneity in our sensitivity analyses. Due to the observational design of the included studies, we cannot conclude about the causal association between PA trajectories and mortality. However, our results are biologically plausible and support temporality, consistency, and strength of the associations.

CONCLUSIONS

By examining trajectories of physical activity in patients with CHD, the findings of this study suggest the

possible protective effect of increased or continued activity and the potential harms of decreased activity or inactive lifestyle. Attention to patients' individual PA trajectories should become routine in clinical practice, and be the object of further, more focused research.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: PA trajectories have prognostic implications for patients with CAD, reflecting comorbidities and functional status.

TRANSLATIONAL OUTLOOK: Further research should explore the interactions of PA trajectories, other health behavior, biomarkers, frailty, and mortality to elucidate physiological pathways and identify patients who benefit from specific interventions to increase activity.

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APPENDIX For supplemental sections, tables, and figures, please see the online version of this paper.