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ORIGINAL RESEARCH ARTICLE

High-Volume Physical Activity and Clinical Coronary Artery Disease Outcomes: Findings From the Cooper Center Longitudinal Study

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BACKGROUND: High-volume physical activity (PA) is associated with a higher prevalence of subclinical coronary artery disease (CAD). However, the clinical significance of subclinical CAD among high-volume exercisers remains incompletely understood, and the dose–response relationship between high-volume PA and clinical CAD events remains uncertain.

METHODS: Individual participant data from the Cooper Center Longitudinal Study (1987–2018) were linked to Medicare claims files. PA volume was determined by self-report and categorized as <500, 500 to 1499, 1500 to 2999, and ≥3000 metabolic equivalent of task (MET)-minutes per week. Subclinical CAD (coronary artery calcium [CAC]) was measured by cardiac computed tomography. All other risk factors were measured in the standard fashion. Composite CAD events (acute myocardial infarction and revascularization) and all-cause mortality were determined from Medicare claims files. A multivariable-adjusted proportional hazards illness-death model with random shared frailty was used to estimate the association between PA volume, CAC, and both clinical CAD and death. Heterogeneity in the association between CAC and clinical CAD across levels of PA was determined with multiplicative interaction terms.

RESULTS: We included 26 724 participants (54 years of age; 28% women). Mean exercise volume was 1130 MET-minutes per week, with 1997 (7.5%) reporting ≥3000 MET-minutes per week. After a mean follow-up of 20.5 years, we observed 811 acute myocardial infarction events, 1636 composite CAD events, and 2857 deaths without CAD. Compared with individuals exercising <500 MET-minutes per week, the lowest risk for acute myocardial infarction occurred among individuals with intermediate PA volumes (500–1499 MET-minutes per week: hazard ratio [HR], 0.77 [95% CI, 0.65–0.91]; 1500–2499 MET-minutes per week: HR, 0.78 [95% CI, 0.63–0.95]). There was no association between high-volume PA (>3000 MET-minutesw per week) and risk for acute myocardial infarction (HR, 0.95 [95% CI, 0.72–1.25]). In contrast, the lowest risk for death was observed among the high-volume PA group (HR, 0.71 [95% CI, 0.60–0.83]). CAC (on log scale) was associated with a higher risk for composite CAD across all PA categories, including among the high-volume PA subgroup (HR, 1.29 [95% CI, 1.16–1.44]; $P<0.001$; $P_{interaction} = 0.969$).

CONCLUSIONS: Compared with low-volume PA, high-volume PA was associated with a lower risk for all-cause mortality but a similar risk for clinical CAD. CAC was associated with an increased risk for clinical CAD regardless of the volume of PA.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atherosclerosis ■ coronary artery disease ■ epidemiology ■ exercise

Editorial, see p XXX

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ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- The lowest risk for clinical coronary artery disease is between 500 and 3000 metabolic equivalent of task (MET)-minutes per week of physical activity.
- Coronary artery calcification is associated with an increased risk for clinical coronary artery disease regardless of the volume of physical activity. The association between coronary artery calcium and clinical coronary artery disease is not modified by the volume of physical activity.

What Are the Clinical Implications?

- There is no apparent additional benefit for coronary artery disease risk reduction for physical activity volumes >3000 MET-minutes per week, or ≈6 times the guideline-recommended amount.
- The presence of coronary artery calcium among high-volume exercisers is clinically significant and should be interpreted as a guide to preventive therapies, similar to elevated coronary artery calcium observed in other clinical contexts.

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
CAC	coronary artery calcium
CAD	coronary artery disease
CCLS	Cooper Center Longitudinal Study
CVD	cardiovascular disease
HR	hazard ratio
MET	metabolic equivalent of task
MI	myocardial infarction
PA	physical activity

Habitual exercise results in a variety of physiological adaptations and is associated with a lower risk for cardiovascular and all-cause mortality.[1–4] Numerous physical activity (PA) guidelines recommend ≥150 minutes per week of moderate-intensity activity or 75 minutes per week of vigorous-intensity activity (or an equivalent combination), corresponding to an overall dose of PA of ≈500 metabolic equivalent of task (MET)-minutes per week.[5,6] However, higher volumes of exercise beyond this threshold are associated with only modestly lower risk for coronary artery disease (CAD).[3,7] In recent years, previous studies have suggested the possibility of an increased risk for clinical events at volumes in excess of 3000 MET-minutes per week (herein defined as high-volume PA), leading to the formation of the "extreme exercise hypothesis,"[1] with the suggestion of a possible association between PA levels above this threshold and clinical CAD events.[8] However, previous studies have been limited by few clinical outcomes specific to clinical CAD among high-volume exercisers, resulting in wide CIs with imprecise estimates of risk for clinical CAD.

Attempts to assess the risk of high-volume exercise have mostly investigated surrogate outcomes such as subclinical coronary atherosclerosis. Multiple previous studies have observed that individuals who report high-volume PA have a higher prevalence of coronary atherosclerosis as measured by cardiac computed tomography.[9–15] However, the significance of this excess burden of coronary atherosclerosis for clinical CAD among high-volume exercisers remains incompletely understood,[16,17] particularly in light of our previous report demonstrating a lower risk for all-cause mortality among high-volume exercisers.[17] The increased proportion of calcified versus noncalcified plaque in studies of competitive athletes[10,12] has raised the possibility that coronary atherosclerosis among high-volume exercisers might not be associated with an increased risk for clinical CAD; however, this hypothesis has not been formally tested. Specifically, it remains unknown whether high-volume PA attenuates the risk of CAD events associated with increased coronary atherosclerosis.

Therefore, we sought to answer 2 important questions related to the potential risks of high-volume exercise. First, what is the dose-response relationship between relatively high volumes of PA and clinical CAD events? Second, does high-volume PA modify the association between subclinical coronary atherosclerosis, as measured by coronary artery calcium (CAC), and clinical CAD? We used the CCLS (Cooper Center Longitudinal Study) to answer these questions because of the unique characteristics of this cohort, including its large size, large number of high-volume exercisers, measured CAC, and clinical CAD outcomes.

METHODS

The CCLS (https://www.cooperinstitute.org/research/ccls) data are not publicly available. The authors will make analytical methods but not data available to other researchers on request.

Study Population

We used the CCLS-Medicare data set, a prospective cohort study that aims to assess the association of lifestyle behaviors with morbidity and mortality.[18–20] Study participants are community-dwelling adults who are self-referred for preventive care or referred to the clinic by their employer. They are predominantly White, are well educated, and have access to medical care. Participants in the CCLS provided written informed consent. The Cooper Institute institutional review board evaluates and approves the CCLS on an annual basis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

We included all participants in the CCLS from 1987 to 2018 with self-reported PA, who were free from coronary disease events before Medicare enrollment, and who were Medicare

eligible at ≥65 years of age. Among 29 747 study participants in the CCLS with subsequent enrollment in Medicare Parts A and B, we excluded 408 individuals with CAD events before Medicare enrollment. We also excluded 2 participants with advanced age (≥90 years), 152 participants with a body mass index ≤18.5 kg/m^2, and 2461 individuals who had missing baseline covariates (PA, body mass index, blood sugar, cholesterol levels, or systolic blood pressure), leaving a final sample of 26 724 individuals. For analyses that included CAC as a covariate, we excluded those participants without measured CAC at the time of the baseline examination, leaving a sample size of 14 071.

Self-Reported Leisure-Time PA

In the Cooper Clinic medical and lifestyle history questionnaire, study participants reported weekly duration (minutes per week) of various leisure-time physical activities in the previous 3 months, and the intensity of each reported activity was assigned according to a standardized MET value.[17,21] Average volume estimates (minutes×intensity) were summed across all reported activities[22] to provide an estimated total leisure-time moderate to vigorous PA volume. Participants were categorized according to the overall volume of PA into 4 mutually exclusive categories, similar to our previous reports[17]: < 500, 500 to 1499, 1500 to 2999, and ≥3000 MET-minutes per week.

Coronary Calcium Measurement

From 1998 through 2008, CAC was assessed by electron beam tomography scan with the C-150XP or C-300 system (GE Imatron, San Francisco, CA). From 2008 to 2018, a 64-slice scanner (Lightspeed VCT, GE Healthcare, Waukesha, WI) was used. During the standard breath-holding protocol, 3-mm-thick slices were obtained with 2-mm table increments. The methods for determining the Agatston calcium score have previously been reported.[23] In this cohort, CAC quantification has been shown to be highly reproducible and free of bias.[24,25]

Other Study Measurements

Details of the baseline clinical examination and the study cohort have previously been described.[18,20] Participants completed a comprehensive examination, including self-reported personal medical and family history, a medical examination by a physician, fasting blood levels of glucose and cholesterol profile, and a maximal treadmill exercise test. Body mass index was determined from measured height and weight with the standard formula.

Study Outcome: Medicare Claims Data

Medicare claims data were obtained from the Centers for Medicare & Medicaid Services for CCLS participants who were ≥65 years of age (Medicare eligible) between 1999 (the first year that Centers for Medicare & Medicaid Services data are available for public use) and 2019, as has been reported in previous articles from CCLS.[19,20] The Centers for Medicare & Medicaid Services contains 100% of fee-for-service claims paid by Medicare for covered health care services. Acute myocardial infarction (AMI) diagnoses were determined from the Chronic Condition Warehouse included in the Master Beneficiary Summary File, which uses at least one inpatient claim for AMI with *International Classification of Diseases, 10th Revision* (or equivalent), code.[26] Inpatient coronary artery revascularization procedures (percutaneous coronary intervention, coronary artery bypass graft) were acquired with established *International Classification of Diseases, 9th Revision, Clinical Modification* and *International Classification of Diseases, 10th Revision, Procedure Coding System* codes from the Medicare provider analysis and review file (Supplemental Material). The a priori primary and secondary outcomes of this study were AMI and composite CAD (AMI+revascularization procedures), respectively. An additional secondary outcome included all-cause mortality. All-cause mortality, but not cause-specific mortality, outcomes are available from Centers for Medicare & Medicaid Services claims files.

Statistical Analyses

Baseline characteristics were compared across PA categories and were tested with Jonckheere-Terpstra (nonparametric) trend statistics. A proportional hazards illness-death model with parametric and sex-specific (Gompertz) baseline survival function and gamma (random) shared frailty effect[27] was used to jointly estimate hazard ratios (HRs) for the semicompeting risks of earliest CAD event, death without CAD, or death after CAD; we report associations between PA and CAD event and all-cause mortality separately. The shared frailty approach allows that loss of follow-up attributable to death may be informative on follow-up for the primary outcome. The parametric baseline survival function permits missing data on current smoking status to be accommodated with maximum likelihood estimation.[28] The primary exposure variable was PA volume, grouped as <500, 500 to 1499, 1500 to 2999, or ≥3000 MET-minutes per week. In separate models, PA volume was entered as a continuous (linear) effect and nonlinearly by expanding in Chebyshev polynomials up to degree 5.[29] Covariates included age, sex, year of midlife preventive medicine examination, current smoking status, body mass index, fasting glucose, total cholesterol, and systolic blood pressure, all assessed at the midlife examination. Additional models were constructed to explore the association between time from clinical examination and Medicare entry on the associations between PA volume and clinical CAD outcomes with multiplicative interaction terms (PA×time). Similar models were constructed to explore sex differences in the association between PA and clinical CAD with multiplicative interaction terms (PA×sex). Unadjusted cumulative incidence curves for both CAD outcomes were determined across PA categories according to selected CAC score thresholds. The joint association between PA and CAC on clinical CAD was evaluated with illness-death models, as done previously, in which PA was similarly categorized and CAC was entered as a continuous variable on the log scale $[\ln(\text{CAC}+1)]$. Heterogeneity in the association between CAC and clinical CAD across levels of PA was determined with a multiplicative interaction term (PA×CAC). All analyses were programmed in SAS/STAT software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

We included 26 724 participants (7508 female [28.1%]; mean±SD age, 53.9±8.9 years). The mean±SD exercise volume across PA levels was 1130±1370

MET-minutes per week, with 7.5% of participants exercising 3000 MET-minutes per week. Baseline characteristics across PA levels are shown in Table 1, demonstrating an overall low burden of cardiovascular risk factors and, as expected, a lower burden of risk factors across higher levels of PA. A similar pattern of results was observed in men and women separately (Tables S1 and S2). Among individuals with CAC available at study entry (n=14 071), we observed similar baseline characteristics and a similar pattern of association between PA volume and CAD risk factors. The mean±SD CAC for the total sample was 208.1±564.3 arbitrary units, with a higher mean CAC across exercise groups. The prevalence of $CAC_{\geq 100}$ was 28.5% among individuals with <500 MET-minutes per week and 34.5% among individuals with ≥3000 MET-minutes per week (P_{trend}<0.001; Table S3).

Associations Between PA Volume and Clinical CAD Events

After a total of 214 538 person-years of follow-up during years of Medicare eligibility, we observed 811 hospitalizations for AMI and 1636 composite CAD events (AMI+revascularization), with an overall event rate of 3.78 and 7.89 per 1000 person-years, respectively. CAD event rates were generally lowest among individuals with intermediate PA volumes (Table 2). After multivariable adjustment, compared with individuals with PA <500 MET-minutes per week, we observed a significantly lower risk for AMI among individuals with PA of 500 to 1499 MET-minutes per week and 1500 to 2999 MET-minutes per week (HR, 0.77 [95% CI, 0.65–0.91]; HR, 0.78 [95% CI, 0.63–0.95], respectively). A similar pattern of results was observed for composite CAD events as well, with a significantly lower risk among individuals with intermediate PA volumes (500–1499 MET-minutes per week: HR, 0.86 [95% CI, 0.76–0.96]; 1500–2999 MET-minutes per week: HR, 0.85 [95% CI, 0.74–0.98]). Compared with participants with PA volume <500 MET-minutes per week, high-volume PA (>3000 MET-minutes per week) was not associated with CAD events (AMI: HR, 0.95 [95% CI, 0.72–1.25]; composite CAD: HR, 0.91 [95% CI, 0.74–1.11]; Table 2). A similar pattern of results was also observed for both AMI and composite CAD among participants with noncontrast cardiac computed tomography performed at baseline (Table S4).

In analyses evaluating the nonlinear associations between PA volume and clinical CAD, we observed a similar pattern of results, with the lowest risk for AMI occurring among individuals with intermediate exercise volumes (Figure 1). For the composite CAD outcome, the lowest risk was also noted among individuals with intermediate exercise volumes (Figure S1).

Table 1. Baseline Characteristics of CCLS Participants According to Categories of PA Volume (n=26 724)

	<500 MET-min/wk (n=9629)	500–1499 MET-min/wk (n=9934)	1500–2999 MET-min/wk (n=5164)	≥3000 MET-min/wk (n=1997)	*P* value
Age at clinic examination, mean±SD, y	54.2±8.8	54.1±8.8	53.2±8.9	52.9±9.2	<0.001
Men, n (%)	6848 (71.1)	7045 (70.9)	3810 (73.8)	1513 (75.8)	<0.001
White, n (%)	9179 (95.3)	9568 (96.3)	4961 (96.1)	1920 (96.1)	<0.001
Current smoker,* n (%)	1395 (14.5)	813 (8.2)	362 (7.0)	127 (6.4)	<0.001
Alcohol consumption, mean±SD, drinks/wk	5.5±7.4	5.8±7.1	6.0±7.1	6.2±7.3	<0.001
BMI, mean±SD, kg/m^2	27.9±4.9	26.2±4.1	25.6±3.7	25.1±3.6	<0.001
Waist circumference, mean±SD, cm	95.7±16.0	90.7±13.1	89.2±12.2	87.1±11.7	<0.001
History of high blood pressure, n (%)	2248 (23.3)	1897 (19.1)	814 (15.8)	271 (13.6)	<0.001
Systolic blood pressure, mean±SD, mm Hg	124.1±15.7	122.6±15.0	122.6±15.2	122.8±15.4	<0.001
Diastolic blood pressure, mean±SD, mm Hg	82.3±10.1	81.2±9.7	81.1±9.7	80.5±9.6	<0.001
History of diabetes, n (%)	309 (3.2)	202 (2.0)	91 (1.8)	25 (1.3)	<0.001
Family history of MI, n (%)	3772 (39.2)	3828 (38.5)	2050 (39.7)	755 (37.8)	<0.001
Glucose, serum, mean±SD, mg/dL	102.6±22.1	99.3±16.2	98.5±15.2	97.6±13.5	<0.001
Total cholesterol, serum, mean±SD, mg/dL	208.8±40.6	205.6±39.3	204.0±37.5	202.1±36.1	<0.001
LDL cholesterol, serum, mean±SD, mg/dL	129.6±36.2	127.5±35.7	126.4±34.2	123.9±33.1	<0.001
Cardiorespiratory fitness,† mean±SD, MET	9.5±2.0	10.9±2.3	12.0±2.5	13.1±2.9	<0.001
Exercise volume, mean±SD, MET-min/wk	125.2±167.5	932.3±283.7	2067.2±414.1	4536.4±2282.1	<0.001
Exercise volume, mean±SD, h/wk	0.4±0.6	2.7±1.0	5.1±1.6	10.5±5.5	<0.001

BMI indicates body mass index; CCLS, Cooper Center Longitudinal Study; LDL, low-density lipoprotein; MET, metabolic equivalent of task; MI, myocardial infarction; and PA, physical activity.

*Data on current smoking missing in 228.

†Data on exercise testing missing in 2761.

Table 2. Multivariable-Adjusted* Associations Between Baseline PA Volume and Clinical CAD in the CCLS (n=26 724)

	Acute MI					MI/CABG/PCI				
MET-min/wk	Medicare person-years	Events	Event rate (per 1000 person-y)	HR (95% CI)	*P* value	Medicare person-years	Events	Event rate (per 1000 person-y)	HR (95% CI)	*P* value
<500	72 127.1	322	4.46	1.0	…	69 694.2	610	8.75	1.0	…
500–1499	82 946.6	280	3.38	0.77 (0.65–0.91)	0.002	80 169.4	595	7.42	0.86 (0.76–0.96)	0.009
1500–2999	43 068.9	143	3.32	0.78 (0.63–0.95)	0.015	41 687.2	307	7.36	0.85 (0.74–0.98)	0.027
≥3000	16 395.7	66	4.03	0.95 (0.72–1.25)	0.709	15 903.2	124	7.80	0.91 (0.74–1.11)	0.330

CABG indicates coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease; CCLS, Cooper Center Longitudinal Study; HR, hazard ratio; MET, metabolic equivalent of task; MI, myocardial infarction; PA, physical activity; and PCI, percutaneous coronary intervention.

*Models were multivariable adjusted for age, sex, year of midlife examination, current smoking status, body mass index, fasting glucose, total cholesterol, and systolic blood pressure.

In sex-stratified analyses, we observed no apparent association between PA and CAD outcomes in women, reflecting the smaller sample size and fewer CAD outcomes in women, resulting in wide CIs. However, there was no evidence of effect modification by sex for AMI ($P_{interaction}$=0.275) or composite CAD ($P_{interaction}$=0.847; Figure S2). Furthermore, we observed no evidence of heterogeneity in the association between PA and CAD outcomes across varying time intervals from PA ascertainment to Medicare enrollment for both AMI (PA×time: $P_{interaction}$=0.667) and composite CAD (PA×time: $P_{interaction}$=0.783).

Associations Between PA Volume and Total Mortality

In contrast to relationships observed between PA volume and CAD events, we observed a more consistent relationship between PA volume and total mortality. Over the same follow-up period, we observed 2857 deaths before CAD-related outcomes, with an overall mortality rate of 13.3 per 1000 person-years. The highest mortality rate was observed among participants with the lowest PA volume (<500 MET-minutes per week), with lower mortality rates observed across higher PA volumes such that we observed the lowest risk among participants with the highest volume of PA (HR, 0.71 [95% CI, 0.60–0.83]; Table S5).

Associations Between CAC and Clinical CAD Events Across PA Subgroups

The presence of CAC was associated with an increased risk for clinical CAD outcomes. Compared with CAC_0, $CAC_{1–99}$ was associated with a nearly 2-fold increased risk for AMI (HR, 1.83 [95% CI, 1.22–2.74]), and $CAC_{\geq 100}$ was associated with a nearly 4-fold increased risk for AMI (HR, 3.75 [95% CI, 2.58–5.46]). A similar pattern of results was observed for composite CAD ($CAC_{1–99}$: HR, 1.88 [95% CI, 1.33–2.66]; $CAC_{\geq 100}$: HR, 5.48 [95% CI, 4.03–7.45]).

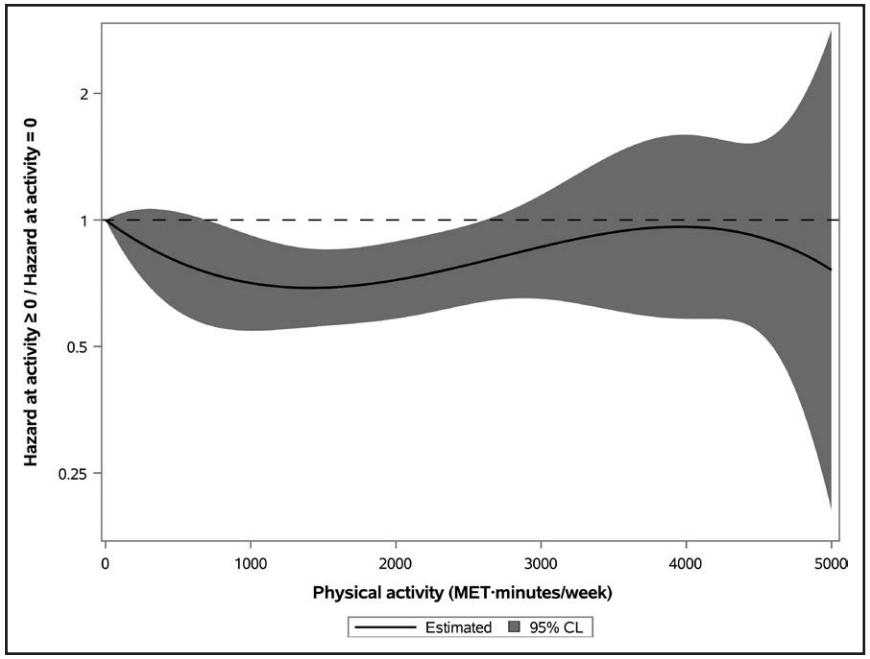

Figure 1. Dose–response relationship between physical activity and AMI. The plot shows how the acute myocardial infarction (AMI) hazard ratio (HR) varies with physical activity at levels ≥0 metabolic equivalent of task (MET)-minutes per week. Physical activity volume was entered as a continuous (linear) effect and nonlinearly by expanding in Chebyshev polynomials in which the hazard observed by individuals who do not engage in leisure-time physical activity is the denominator of the HR. Models were multivariable adjusted for age, sex, year of midlife examination, current smoking status, body mass index, fasting glucose, total cholesterol, and systolic blood pressure. CL indicates confidence limit.

The association between CAC and AMI appeared similar across categories of PA volume. These findings were consistent across different thresholds for CAC. For example, CAC ≥100 (compared with CAC <100) was associated with a higher cumulative incidence for AMI in both low-volume exercisers (PA <500 MET-minutes per week: log-rank P<0.001) and high-volume exercisers (PA ≥3000 MET-minutes per week: log-rank P=0.016; Figure 2A). A similar pattern of results was observed for associations with composite CAD outcomes (Figure 2B) and when CAC was categorized at zero versus nonzero (Figure S3).

In multivariable-adjusted models, when CAC was evaluated as a continuous variable on the log scale, higher CAC was associated with a similar risk among individuals with PA <500 MET-minutes per week (HR [per doubling of CAC], 1.21 [95% CI, 1.15–1.28]) and among individuals with PA >3000 MET-minutes per week (HR, 1.20 [95% CI, 1.06–1.36]) with no evidence of effect modification by PA level ($P_{interaction}$=0.508; Figure 3A). A similar pattern of results was observed for composite CAD outcomes, with a similar association between CAC and composite CAD outcomes across levels of PA volume ($P_{interaction}$=0.969; Figure 3B). In analyses stratified by sex, the association between CAC and CAD outcomes was similar in men and women (Tables S6 and S7).

DISCUSSION

In the present study, we observed 2 important findings. First, we observed that CAC was consistently associated with clinical CAD outcomes across a broad range of PA levels with no evidence of effect modification. These findings suggest that the clinical significance of elevated CAC in high-volume exercisers is similar to that of elevated CAC observed in other contexts. Second, compared with PA below the guideline-recommended amount, intermediate levels of PA were associated with a significantly lower risk for clinical CAD. The risk for clinical CAD was similar between participants who reported low PA and participants who reported high-volume PA levels. In contrast, we observed a different pattern of results for all-cause mortality, with a more consistent association between higher volumes of PA and lower mortality, even among high-volume exercisers. Taken together, these findings suggest that although there is no evidence of an increased risk for mortality, there appears to be a limit to

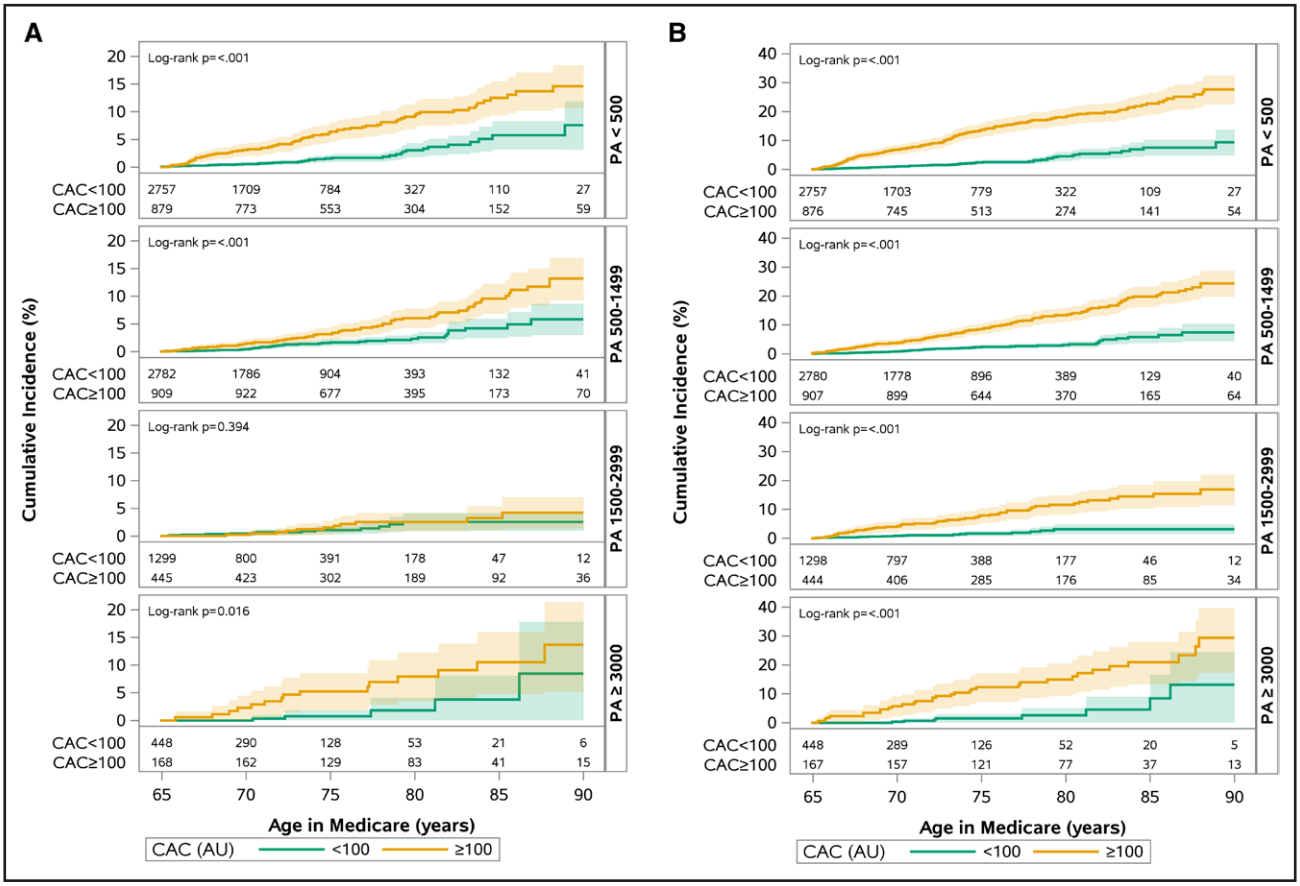

Figure 2. Unadjusted cumulative incidence curves.
Unadjusted cumulative incidence curves according to baseline coronary artery calcium (CAC) score (≥100 vs <100) stratified by self-reported levels of physical activity (PA) for acute myocardial infarction (AMI; **A**) and composite coronary artery disease outcomes (AMI, percutaneous coronary intervention, and coronary artery bypass graft; **B**). AU indicates arbitrary units.

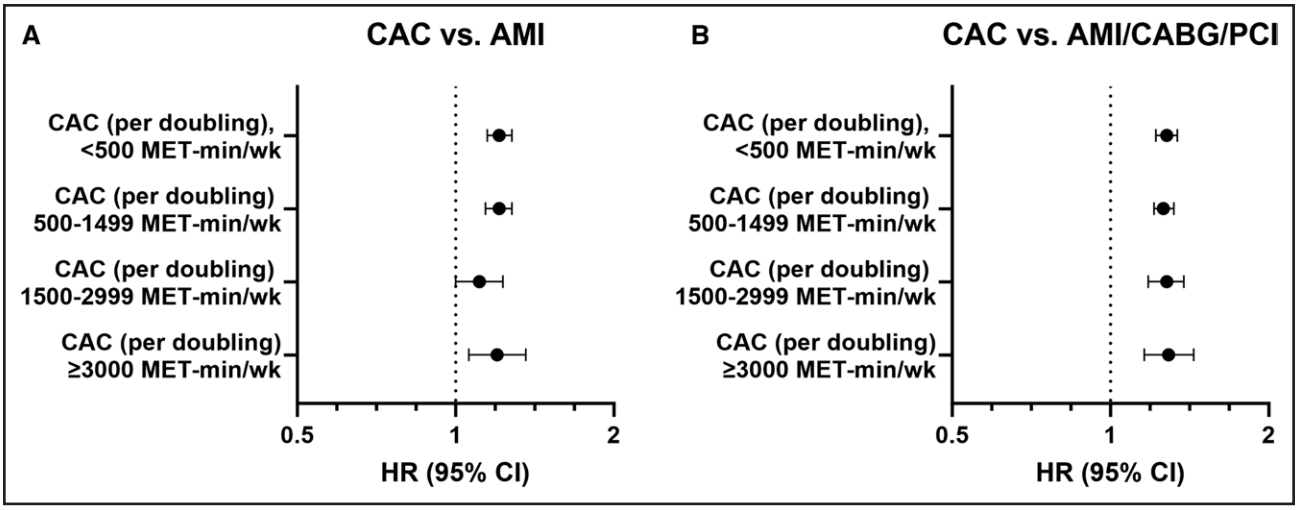

Figure 3. Xxx.

A, Multivariable-adjusted association between coronary artery calcium (CAC) and acute myocardial infarction (AMI) across levels of self-reported physical activity (PA). CAC was modeled on log scale as a continuous variable, stratified according to baseline PA ($P_{interaction}$ [PA×CAC]=0.508). **B**, Multivariable-adjusted association between CAC and composite coronary artery disease (AMI/percutaneous coronary intervention [PCI]/coronary artery bypass graft [CABG] across levels of self-reported PA; n=14 701). CAC was modeled on log scale as a continuous variable ($P_{interaction}$ [PA×CAC]=0.969). Multivariable adjustment as in Figure 1.

the benefit of PA for the reduction of CAD risk at levels beyond 3000 MET-minutes per week.

Current Study in Context

Physical inactivity is a well-recognized risk factor, and observational data have shown for decades that higher levels of self-reported PA are associated with a lower risk for mortality.[3,30,31] These consistent observations have informed clinical practice guidelines that recommend a minimum of 150 minutes per week of moderate-intensity exercise or 75 minutes per week of vigorous-intensity exercise.[32] However, because the dose-response relationship between exercise volume and mortality appears to asymptote beyond these levels, guidelines have not recommended exercise volumes more than twice the recommended amount for substantial health benefits.

The observation in the present study that high volumes of PA do not provide additional clinical benefit for CAD risk reduction is not inconsistent with a previous report from the CCLS.[17] First, similar to the present article, we previously reported that high volumes of PA were associated with a decreased risk for all-cause mortality. Second, this previous report was limited to only cardiovascular disease (CVD) mortality and did not include nonfatal clinical CAD events. CVD mortality is a heterogeneous phenotype that reflects mechanisms of CVD beyond CAD such as structural heart disease. Furthermore, CVD mortality outcomes derived from death certificates are well known to have limitations, particularly among older adults for whom non-CVD deaths are commonly categorized as CVD deaths.[33] In the present report, we were able to characterize the association of high-volume exercise more specifically with clinical CAD events (AMI, percutaneous coronary intervention, and coronary artery bypass graft) using linkage to Medicare claims files. Given previous reports of an increased burden of coronary atherosclerosis in this population,[10] we believe these to be the most appropriate clinical outcomes of interest. Third, previous reports from our group have been underpowered to detect differences in CVD outcomes because of relatively few events. For example, we previously reported no association between lower PA volumes (<1500 MET-minutes per week) and either moderate (1500–2999 MET-minutes per week) or high-volume (≥3000 MET-minutes per week) exercise on CVD mortality. However, among participants with PA ≥1500 MET-minutes per week, this previous report was limited to only 28 total CVD deaths compared with 431 CAD events in this subgroup in the present report. This much larger number of events allows us to extend these previous observations, reporting that moderate levels of PA (500–1499 and 1500–2999 MET-minutes per week) are associated with a significantly lower risk for CAD events. However, even with 124 events among high-volume exercisers, CAD risk was not significantly different from that of participants exercising at or below guideline-recommended amounts.

Potential Mechanisms

The higher burden of coronary atherosclerosis among high-volume exercisers is one potential mechanism for the apparent discordance between clinical CAD events and mortality. Higher volumes of exercise are associated with many salutary benefits, including a lower risk of typical risk factors such as diabetes, dyslipidemia, obesity, and hypertension.[32] Indeed, much of the benefits of PA

are mediated through favorable effects on these risk factors.[34] Higher volumes of exercise are also associated with more direct effects on the cardiovascular system, including improved coronary vasodilatory capacity[22,35] and endothelial function,[36–38] reduced arterial stiffness/vascular age,[39] decreased inflammation and thrombotic potential,[37] and increased vagal tone.[40] Both animal[41] and human[42] studies have also shown slowing and even regression of atherosclerosis with moderate to high volumes of exercise.

Nevertheless, despite these effects of exercise, recent data suggest that volumes of exercise much greater than guideline-recommended amounts promote atherosclerosis directly, in contrast to more moderate exercise doses, which have been shown to attenuate the atherosclerotic process.[41] In 3 separate studies, lifelong, high-volume exercisers were shown to have a higher burden of coronary atherosclerosis.[10,12,14] In the more recent Master@Heart Study,[14] these associations appeared most prominent among those participating in high-volume exercise across the life span (36 years of exercise) compared with late-onset, high-volume exercisers (14 years of exercise). Specifically, lifelong, high-volume exercise was associated with a higher burden of both calcified and noncalcified plaque, including coronary atherosclerosis phenotypes known to be associated robustly with CAD risk, including proximal, noncalcified plaques. Although our data do not allow an exploration of the underlying mechanisms accounting for our observations, we believe that the nadir in risk for CAD events at intermediate levels of PA reflects the convergence of 2 different pathophysiological mechanisms, in which the protective effect of PA on the atherosclerotic process observed at moderate levels of exercise is attenuated by the negative effect of high volumes of PA.

The cumulative effects of acute exercise could also explain our observation that high-volume exercise is not associated with a lower risk for clinical CAD.[43] In a seminal report from Mittleman et al,[44] vigorous exercise sessions were associated with a transient increase in risk for myocardial infarction. Although the acute effects of exercise were most apparent among sedentary individuals, there was still a modest, transient increase in risk for myocardial infarction among frequent exercisers. Given that high-volume exercisers are exercising more frequently, it is possible that their higher cumulative exposure to this transient increase in myocardial infarction risk accounts for the similar risk in high-volume and sedentary participants in our study.

Implications of Coronary Atherosclerosis in High-Volume Exercisers

Before the present study, the clinical relevance of the increased burden of coronary atherosclerosis in high-volume exercisers has been uncertain, reflecting the limited number of clinical CAD outcomes in cohorts with sufficient numbers of well-phenotyped, high-volume exercisers.[45,46] In a previous report from the CCLS, we observed that CAC and fitness were independent predictors of risk for CVD.[25] Although we observed that the absolute risk for CVD was greatest among individuals with both elevated CAC and low cardiorespiratory fitness, we also observed that the relative risk reduction for fitness was consistent across all levels of CAC and that there was no qualitative interaction between fitness and CAC on CVD outcomes ($P_{interaction}$=0.689). It is important to note that the independence of CAC and fitness is also consistent with the conclusion that CAC is associated with CVD risk across the distribution of fitness levels, and no level of fitness provides immunity from CAD events. In the present report, we extend this previous observation to self-reported PA, demonstrating that the relative risk related to elevated CAC is not modified by higher levels of self-reported PA.

Our results suggest that the presence of CAC among high-volume exercisers is not a benign phenotype. If elevated CAC in this group were truly benign, we would have expected that elevated CAC would be differentially associated with CAD risk across the range of exercise volumes, with an attenuation in risk attributed to CAC among high-volume exercisers. Rather, we observed that CAC was associated with a similar increase in clinical CAD events among both physically inactive and high-volume exercisers with no evidence of effect modification.

This finding has several clinical implications. First, elevated CAC in the setting of high-volume exercise should be treated similarly to other scenarios with elevated CAC and in accordance with clinical practice guidelines wherein statin therapy should be initiated, particularly among those with CAC ≥100 or ≥75th percentile.[47] Second, high-volume exercise does not prevent the atherosclerotic process and should be considered part of the shared decision-making discussion to determine the merits of statin therapy initiation among patients at borderline or intermediate risk for atherosclerotic CVD. At a minimum, clinicians could consider CAC testing in the setting of high-volume exercise, particularly if it might change clinical decision-making.

Limitations

Several potential limitations should be noted. First, we included self-reported rather than objectively measured PA. Although this could have contributed to misclassification of PA, resulting in some attenuation of the observed associations between PA and CHD events, we believe that the use of self-report PA levels has an important added advantage for several reasons. First, we were most interested in leisure-time PA at the level commonly reported among high-volume exercisers who have been

recruited to participate in previous studies of coronary atherosclerosis. High doses of PA acquired throughout the day through an active lifestyle are likely to have substantially different effects on the cardiovascular system, as noted in previous reports that have shown that a high level of total PA has a much different dose-response relationship with CVD outcomes compared with recreational activity.[48] Therefore, we believe that this method of PA ascertainment is to be preferred over other methods to address this question.

Second, there was an ≈12-year gap between PA ascertainment and Medicare enrollment. We believe that this most likely attenuated the observed associations between PA and clinical CHD given the likely downstream changes in PA patterns leading to misclassification and bias toward the null. We see evidence of this in our present analysis. When we evaluated the association between PA and CHD outcomes in the CAC cohort who had a shorter gap (8 years), we observed an association between intermediate PA and CHD risk (52% risk reduction) that appeared stronger than that observed in the larger cohort (22% risk reduction). Furthermore, we observed no impact of time between clinical examination and Medicare enrollment on the associations between PA and CAD events, further supporting that this time gap did not affect our findings.

Third, the CCLS is an overall healthy cohort with higher-than-average PA behaviors relative to the general population. Although this cohort may not represent the general population, we believe that it is the optimal cohort to test the hypothesis of the present study. Furthermore, the ability to characterize the impact of PA volumes with a low background burden of traditional CAD risk factors provides a unique opportunity to explore the true impact of PA on CAD outcomes without the confounding effects of marked differences in risk factors across PA groups that are commonly present in other studies.

Conclusions

In a large cohort with a relatively high prevalence of high-volume exercisers, we observed that intermediate doses of PA were associated with the lowest risk for clinical CAD events. We also observed that prevalent CAC was associated with a similar risk for CAD events across all strata of PA, suggesting that elevated CAC in high-volume exercisers is clinically relevant and should be treated similarly to CAC identified in other contexts.

ARTICLE INFORMATION

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Supplemental Material

Expanded Methods
Tables S1–S7
Figures S1–S3

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