Association of All-Cause and Cardiovascular Mortality With High Levels of Physical Activity and Concurrent Coronary Artery Calcification

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IMPORTANCE Few data are available to guide clinical recommendations for individuals with high levels of physical activity in the presence of clinically significant coronary artery calcification (CAC).

OBJECTIVE To assess the association among high levels of physical activity, prevalent CAC, and subsequent mortality risk.

DESIGN, SETTING, AND PARTICIPANTS The Cooper Center Longitudinal Study is a prospective observational study of patients from the Cooper Clinic, a preventive medicine facility. The present study included participants seen from January 13, 1998, through December 30, 2013, with mortality follow-up through December 31, 2014. A total of 21 758 generally healthy men without prevalent cardiovascular disease (CVD) were included if they reported their physical activity level and underwent CAC scanning. Data were analyzed from September 26, 2017, through May 2, 2018.

EXPOSURES Self-reported physical activity was categorized into at least 3000 (n = 1561), 1500 to 2999 (n = 3750), and less than 1500 (n = 16 447) metabolic equivalent of task (MET)–minutes/week (min/wk). The CAC scores were categorized into at least 100 (n = 5314) and less than 100 (n = 16 444) Agatston units (AU).

MAIN OUTCOMES AND MEASURES All-cause and CVD mortality collected from the National Death Index Plus.

RESULTS Among the 21 758 male participants, baseline mean (SD) age was 51.7 (8.4) years. Men with at least 3000 MET-min/wk were more likely to have prevalent CAC of at least 100 AU (relative risk, 1.11; 95% CI, 1.03-1.20) compared with those accumulating less physical activity. In the group with physical activity of at least 3000 MET-min/wk and CAC of at least 100 AU, mean (SD) CAC level was 807 (1120) AU. After a mean (SD) follow-up of 10.4 (4.3) years, 759 all-cause and 180 CVD deaths occurred, including 40 all-cause and 10 CVD deaths among those with physical activity of at least 3000 MET-min/wk. Men with CAC of less than 100 AU and physical activity of at least 3000 MET-min/wk were about half as likely to die compared with men with less than 1500 MET-min/wk (hazard ratio [HR], 0.52; 95% CI, 0.29-0.91). In the group with CAC of at least 100 AU, men with at least 3000 MET-min/wk did not have a significant increase in all-cause mortality (HR, 0.77; 95% CI, 0.52-1.15) when compared with men with physical activity of less than 1500 MET-min/wk. In the least active men, those with CAC of at least 100 AU were twice as likely to die of CVD compared with those with CAC of less than 100 AU (HR, 1.93; 95% CI, 1.34-2.78).

CONCLUSIONS AND RELEVANCE This study suggests there is evidence that high levels of physical activity (≥3000 MET-min/wk) are associated with prevalent CAC but are not associated with increased all-cause or CVD mortality after a decade of follow-up, even in the presence of clinically significant CAC levels.
The health benefits of regular physical activity are well known, including decreased all-cause mortality, fatal and nonfatal cardiovascular disease (CVD) events, and sudden cardiac death. However, the adverse effects of high levels of endurance activity (well beyond current physical activity guidelines for health promotion) on the development of subclinical coronary artery atherosclerosis have been the focus of recent publications. In a study evaluating 152 masters athletes and 92 controls with low atherosclerotic risk profiles, a small percentage of male athletes (12 of 106 [11.3%]) had coronary artery calcification (CAC) of at least 300 Agatston units (AU), whereas no male controls had similar CAC levels. Whether these data are sufficiently robust to support the conclusion that “coronary plaques are more abundant in athletes” is controversial. Another study evaluating 284 active men showed that those with the highest volume of physical activity (>2000 metabolic equivalent of task [MET]-minutes/week [min/wk]) had a higher prevalence of CAC. In these studies, the dominant plaque morphologic feature (calcified, noncalcified, or mixed) in the most active group was more likely to be calcified plaques, suggesting that these plaques might be more stable and less prone to rupture. These and similar observational studies with small numbers of highly select individuals have demonstrated conflicting results related to subclinical atherosclerosis prevalence. Importantly, primary clinical outcomes are unavailable for these studies, making their clinical implications uncertain.

Few published reports present mortality outcomes in individuals with high levels of endurance activity in the presence of clinically significant CAC and thus, few data are available to guide clinical recommendations. If endurance athletes with higher amounts of CAC demonstrate increased mortality, then consideration should be given to reducing physical activity levels closer to those of the guidelines. Conversely, if the presence of CAC in athletes is not associated with increased mortality, then reassurance regarding high levels of physical activity would be more appropriate.

The objectives of this work were 2-fold: first, to assess the cross-sectional association of prevalent CAC with high levels of physical activity in a large population of generally healthy men, and second, to evaluate whether high levels of physical activity were associated with increased mortality in those with CAC because whether the mild increase in CAC seen in endurance athletes translates to greater mortality remains unknown. Ultimately, the overarching goal of these analyses is to provide clarity for health care professionals and patients regarding the risk of high levels of physical activity in the presence of subclinical atherosclerosis.

### Methods

#### Study Population

The Cooper Clinic, Dallas, Texas, is a preventive medicine practice begun in 1970 that focuses on lifestyle modification for optimal health. This model has motivated endurance athletes and those with considerable routine moderate to vigorous physical activity to seek care at the clinic. In general, the patient population is white and educated and has access to medical care. The Cooper Center Longitudinal Study (CCLS) is a prospective study initiated to evaluate the association between cardiorespiratory fitness (CRF), physical activity, and health. Data collected at the Cooper Clinic and captured in the CCLS database are not based on a systematic research protocol but rather on clinical practices and patient-specific physician recommendations. Clinic patients sign informed consent for the use of their deidentified clinical data for research. The study is approved annually by the institutional review board of The Cooper Institute.

For this study, individuals with an evaluation including history of physical activity and CAC scanning were identified as the base cohort (28 880 men seen from January 13, 1998, through December 30, 2013, with follow-up completed on December 31, 2014). Exclusion criteria for the primary cohort included being younger than 40 years or older than 80 years (n = 2828), follow-up of less than 1 year from scan visit (n = 3144), preexisting myocardial infarction (n = 316) or stroke (n = 112); missing body mass index (BMI); calculated as weight in kilograms divided by height in meters squared) or measurements of blood pressure, glucose levels, triglyceride levels, and high density lipoprotein (HDL) cholesterol levels (n = 704); or a BMI of less than 18.5 (n = 18). These exclusions resulted in a final sample of 21 758 men. A subcohort of 18 564 men underwent treadmill exercise testing to determine CRF for corroboration with self-reported physical activity.

Women were excluded from the primary assessment owing to insufficient number of deaths, which is the primary outcome of interest. Of note, 9501 women remained after the exclusion criteria were applied. In this cohort, only 5 all-cause and 3 CVD deaths occurred in the highly active group of women (≥3000 MET-min/wk). However, because this question is important in men and women, the characteristics, CAC prevalence, and mortality tables for women are included as eTables 1 to 3 and the eFigure in the Supplement.

#### Clinical Status

The baseline examination included a thorough history questionnaire with medical and physical activity questions confirmed by the clinic physician. Prescription medications, including statins, were captured from the physician report. Dietary history was not
Coronary Artery Calcification

Coronary artery calcification as assessed by electron beam tomography scan using the C-150XP or C-300 system (GE Imatron) from 1998 through 2007. Three-millimeter thick slices were obtained with 2-mm table increments during a breath-holding protocol. The methods for determining the Agatston calcium score have been reported. Coronary artery calcification quantification in this cohort is highly reproducible and free of bias. From 2008 to 2013, a 64-section scanner (Lightspeed VCT; GE Healthcare) was used. For the primary analysis, CAC was characterized dichotomously as less than 100 AU vs at least 100 AU to create lower- and higher-risk categories. In addition, CAC of 0 vs CAC of greater than 0 and CAC of less than 400 and CAC of at least 400 were evaluated.

Mortality

Mortality events, including the specific cause of death, were ascertained through 2014 using National Death Index Plus. Cardiovascular death was classified with International Classification of Diseases, Ninth Revision, (deaths through 1999), codes 390 to 449, or International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (deaths after 1999), codes 100 to 199. Follow-up times of participants who were still living at the end of 2014 were right censored.

Descriptive characteristics are presented in Table 1 by physical activity and CAC level categories. In this sample of 21758 men, the mean (SD) age at baseline examination was 51.7 (8.4) years, and most did not use tobacco (86.0%) or a statin medication (82.8%).
Table 1. Baseline Characteristics of 21 758 Generally Healthy Men by Physical Activity Level and CAC Categories*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Physical Activity Category, MET-min/wk</th>
<th>CAC &lt;100 AU</th>
<th>CAC ≥100 AU</th>
<th>P Value for Trend</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>&lt;1500 (n = 12 413)</td>
<td>49.5 (7.1)</td>
<td>50.0 (7.2)</td>
<td>.07</td>
<td>58.7 (8.5)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>1500-2999 (n = 2902)</td>
<td>49.2 (7.0)</td>
<td>50.4 (7.2)</td>
<td>.07</td>
<td>57.9 (8.2)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>≥3000 (n = 11 229)</td>
<td>50.0 (7.2)</td>
<td>50.8 (8.2)</td>
<td>&lt;.001</td>
<td>58.9 (8.5)</td>
</tr>
<tr>
<td>Statin use, No. (%)</td>
<td>&lt;1500 (n = 4034)</td>
<td>11.196 (90.2)</td>
<td>1021 (90.4)</td>
<td>.07</td>
<td>775 (91.4)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>1500-2999 (n = 848)</td>
<td>2616 (90.1)</td>
<td>98 (11.6)</td>
<td>&lt;.001</td>
<td>47 (11.6)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>≥3000 (n = 848)</td>
<td>123.4 (13.3)</td>
<td>127.7 (13.3)</td>
<td>&lt;.001</td>
<td>129.5 (16.1)</td>
</tr>
<tr>
<td>Glucose level, mean (SD), mg/dL</td>
<td>&lt;1500 (n = 2902)</td>
<td>99.8 (19.1)</td>
<td>97.3 (14.1)</td>
<td>&lt;.001</td>
<td>104.9 (23.4)</td>
</tr>
<tr>
<td>Cholesterol level, mean (SD), mg/dL</td>
<td>1500-2999 (n = 11 229)</td>
<td>199.3 (36.5)</td>
<td>196.4 (35.2)</td>
<td>&lt;.001</td>
<td>195.5 (40.7)</td>
</tr>
<tr>
<td>LDL cholesterol level, mean (SD), mg/dL</td>
<td>≥3000 (n = 11 229)</td>
<td>123.9 (32.1)</td>
<td>121.2 (30.8)</td>
<td>&lt;.001</td>
<td>119.1 (35.4)</td>
</tr>
<tr>
<td>HDL cholesterol level, mean (SD), mg/dL</td>
<td>&lt;1500 (n = 4034)</td>
<td>48.1 (12.2)</td>
<td>51.8 (13.2)</td>
<td>&lt;.001</td>
<td>48.2 (12.9)</td>
</tr>
<tr>
<td>Triglyceride level, mean (SD), mg/dL</td>
<td>1500-2999 (n = 848)</td>
<td>140.2 (103.1)</td>
<td>119.3 (87.1)</td>
<td>&lt;.001</td>
<td>146.0 (81.4)</td>
</tr>
<tr>
<td>Calcium level, mean (SD), mg/dL</td>
<td>≥3000 (n = 848)</td>
<td>9.2 (0.4)</td>
<td>9.2 (0.4)</td>
<td>&lt;.001</td>
<td>9.2 (0.4)</td>
</tr>
<tr>
<td>Framingham Risk Score, mean (SD)</td>
<td>&lt;1500 (n = 12 413)</td>
<td>8.7 (5.4)</td>
<td>7.4 (4.7)</td>
<td>&lt;.001</td>
<td>13.5 (8.0)</td>
</tr>
<tr>
<td>Physical activity level, mean (SD), MET</td>
<td>1500-2999 (n = 2902)</td>
<td>343.8 (142.7)</td>
<td>277.9 (146.7)</td>
<td>&lt;.001</td>
<td>430.7 (470.2)</td>
</tr>
<tr>
<td>Physical activity, mean (SD), min/wk</td>
<td>≥3000 (n = 11 229)</td>
<td>104.0 (115.8)</td>
<td>334.4 (179.2)</td>
<td>&lt;.001</td>
<td>105.2 (157.6)</td>
</tr>
<tr>
<td>Lifetime physical activity, mean (SD), y</td>
<td>&lt;1500 (n = 4034)</td>
<td>18.1 (13.3)</td>
<td>22.8 (13.6)</td>
<td>&lt;.001</td>
<td>20.1 (15.2)</td>
</tr>
<tr>
<td>CAC score, mean (SD), AU</td>
<td>1500-2999 (n = 848)</td>
<td>11.3 (22.7)</td>
<td>10.3 (21.5)</td>
<td>.046</td>
<td>736.1 (975.9)</td>
</tr>
<tr>
<td>Calcification volume score, mean (SD)</td>
<td>≥3000 (n = 848)</td>
<td>11.0 (28.7)</td>
<td>10.2 (18.2)</td>
<td>.046</td>
<td>442.9 (539.8)</td>
</tr>
<tr>
<td>No. of calcification lesions, mean (SD)</td>
<td>&lt;1500 (n = 4034)</td>
<td>1.1 (2.1)</td>
<td>1.0 (1.7)</td>
<td>.41</td>
<td>12.5 (12.8)</td>
</tr>
<tr>
<td>Cardiorespiratory fitness, mean (SD), MET</td>
<td>1500-2999 (n = 848)</td>
<td>11.0 (1.9)</td>
<td>12.4 (2.0)</td>
<td>&lt;.001</td>
<td>10.1 (2.0)</td>
</tr>
<tr>
<td>VO2max, mean (SD), mL/kg/min</td>
<td>≥3000 (n = 848)</td>
<td>30.6 (6.8)</td>
<td>43.3 (7.0)</td>
<td>&lt;.001</td>
<td>35.4 (8.0)</td>
</tr>
<tr>
<td>VO2max ≥50 mL/kg/min, No. (%)</td>
<td>&lt;1500 (n = 4034)</td>
<td>571 (5.3)</td>
<td>439 (16.9)</td>
<td>&lt;.001</td>
<td>68 (2.2)</td>
</tr>
<tr>
<td>Maximum heart rate, mean (SD), bpm</td>
<td>1500-2999 (n = 848)</td>
<td>174.8 (13.4)</td>
<td>174.7 (12.6)</td>
<td>.02</td>
<td>165.0 (14.9)</td>
</tr>
<tr>
<td>Heart rate recovery at 1 min, mean (SD), bpm</td>
<td>≥3000 (n = 848)</td>
<td>23.1 (7.5)</td>
<td>24.9 (7.9)</td>
<td>&lt;.001</td>
<td>21.8 (8.2)</td>
</tr>
</tbody>
</table>

Abbreviations: AU, Agatston units; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); bpm, beats per minute; CAC, coronary artery calcification; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task; VO2max, maximum oxygen consumption.  
Si conversion factors: To convert calcium to millimoles per liter, multiply by 0.25; cholesterol to millimoles per liter, multiply by 0.25; glucose to millimoles per liter, multiply by 0.0555; triglycerides to millimoles per liter, multiply by 0.013.  
*Sample sizes were reduced where a specific observation was missing with resulting minimum sample sizes for statin use (n = 20 239), LDL cholesterol level (n = 21 461), calcium level (n = 14 437), lifetime physical activity (n = 13 802), calcification volume (n = 19 411), number of calcifications (n = 19 480), cardiorespiratory fitness (n = 18 564), VO2max (n = 18 564), maximum heart rate (n = 18 564), and heart rate recovery (n = 18 564).  

Men in the most highly active category (>3000 MET-min/wk) were slightly older, were less likely to smoke, had lower BMI and blood glucose and triglyceride levels, and had higher HDL cholesterol levels. The mean physical activity volume in the most highly active group was slightly more than 4600 MET-min/wk, which is equivalent to running 6 miles/day at a pace of 10 minutes per mile (9.6 kilometers/day at a pace of 10 minutes per 1.6 kilometers). This exercise volume is consistent with the weekly distances proposed for and practiced by many masters marathon runners.22  

The lifetime activity in years increased with increasing physical activity category. Coronary artery calcification score, lesion number, and total volume demonstrated no significant trend across physical activity groups within groups with CAC of at least 100 and less than 100 AU.  

Figure 1 shows the sample distribution of physical activity categories in MET-min/wk, with a high-resolution distribution of the most active group. eTable 4 in the Supplement shows the distribution of activities in MET-min/wk by CAC and
results. Of note, the highest activity levels are not limited to running or any single activity. A subgroup analysis of those with an additional physical activity assessment within 5 years of baseline found 61.3% of those with physical activity of at least 3000 MET-min/wk at baseline had confirmation of ongoing high levels of physical activity of at least 1500 MET-min/wk. In 18,564 men with CRF measurement (Table 1), the most highly active group were more fit (mean [SD] METS, 12.9 [2.3] or 44.1 [8.1] mL−1 × kg−1 × min−1) and more likely to have an estimated maximal oxygen consumption of at least 50 mL−1 × kg−1 × min−1 than the less active groups.

Figure 2 summarizes the relative risk of prevalent CAC by physical activity group. Men with at least 3000 MET-min/wk were more likely to have prevalent CAC of at least 100 AU (relative risk, 1.11; 95% CI, 1.03-1.20) compared with those accumulating lesser amounts of physical activity. The number of all-cause and CVD deaths and associated incidence rates are described in Table 2. During a mean (SD) follow-up of 10.4 (4.3) years, 759 men died, including 180 CVD deaths. Among those with physical activity of at least 3000 MET-min/wk, 40 all-cause and 10 CVD deaths occurred.

Age- and multivariate-adjusted analyses revealed 1 statistically significant association among physical activity, CAC, and all-cause mortality (Table 3). In men with CAC of less than 100 AU, those who accumulated at least 3000 MET-min/wk were about half as likely to die compared with men with less than 1500 MET-min/wk (HR, 0.52; 95% CI, 0.29-0.91). In the group with CAC of at least 100 AU, men who accumulated at least 3000 MET-min/wk did not have an increase in all-cause mortality (HR, 0.77; 95% CI, 0.52-1.15) when compared with men with less than 1500 MET-min/wk. When evaluating the association among high physical activity, CAC, and mortality with other CAC cut points, a similar outcome was seen (eTable 5 and 6 in the Supplement), including a statistically significant decrease in all-cause mortality in the highest physical activity group with CAC of at least 1.00 AU (HR, 0.63; 95% CI, 0.44-0.92). Of note, increasing physical activity was not associated with a statistically significant increase in mortality, and no evidence suggested that physical activity hazards for all-cause mortality varied by category of CAC for physical activity of 1500 to less than 3000 MET-min/wk (HR for <1.00 AU, 0.78 [95% CI, 0.56-1.07] vs HR for ≥1.00 AU, 0.87 [95% CI, 0.65-1.17]) and for physical activity of at least 3000 MET-min/wk (HR for <1.00 AU, 0.52 [95% CI, 0.29-0.91] vs HR for ≥1.00 AU, 0.77 [95% CI, 0.52-1.15]; P = .47 for interaction). Similar observations were observed for CVD mortality by category of CAC (physical activity of 1500 to <3000 MET-min/wk: HR for <1.00 AU, 0.66 [95% CI, 0.49-1.21] vs HR for ≥1.00 AU, 0.74 [95% CI, 0.76-1.23]; physical activity of ≥3000 MET-min/wk: HR for <1.00 AU, 0.39 [95% CI, 0.08-1.79] vs HR for ≥1.00 AU, 0,80 [95% CI, 0.39-1.64]; P = .70 for interaction) (see Table 3 for details). Finally, a subgroup analysis was performed with those individuals (n = 20,239) who had medications reported in the study data to evaluate the potential association with statins. Again, HR of less than 1.00 was seen in the high physical activity group after adjusting for statin use (eTable 7 in the Supplement).

Discussion

In this large cohort of men with more than a decade of follow-up, adjusted risk of CAC of at least 100 AU was 11% greater among individuals with very high levels of physical activity compared to those with lower levels. More importantly, no evident association existed between very high levels of physical activity and increased mortality among individuals with and without clinically relevant levels of subclinical atherosclerosis. Indeed, in virtually every analysis, at any cut point of CAC or when considered continuously, individuals with the highest levels of physical activity had lower mortality than those with the lowest activity levels. These results do not support the contention that high-volume endurance activity, with a mean of more than 1 hour of activity per day, increases the risk of all-cause or CVD mortality, regardless of CAC.
Recent studies have raised the possibility that these levels of physical activity and coronary atherosclerosis, but again, these studies include small groups of athletes. Two recent studies \(3,5\) have suggested that extreme levels of physical activity, including marathon running, are associated with increased CAC. However, data evaluating high-volume activity athletes with known CAC and long-term clinical outcomes are scarce. Once CAC is discovered, a great clinical concern is whether continued high levels of activity accelerate the transition to clinical disease, including nonfatal and fatal CVD events. In the present study, although highly active men had slightly greater risk of CAC of at least 100 AU, a corresponding greater mortality was not seen.

Several studies have evaluated the joint effects of CAC and physical activity or CRF, a marker of habitual physical activity, on health outcomes. \(^1\) A large \(N = 10690\) study \(12\) assessed regular physical activity with a low resolution scale from 0 to 10 (0 indicates never; 10, all the time) and demonstrated all-cause mortality was higher with lower activity and higher CAC. With respect to CRF, in a study of 25,972 middle-aged Korean individuals with CAC and CRF measurements who were followed up for 5.5 years, \(^31\) those with more than 10-MET CRF (vs lower CRF) had an attenuated association of high CAC with all-cause mortality. Recently, Radford et al \(^32\) evaluated more than 8000 healthy men and found that for any baseline age and CAC level, higher CRF was associated with lower annual total CVD incidence. Although these studies evaluated large numbers of individuals, they did not focus on the high levels of physical activity and coronary atherosclerosis, but again, these studies include small groups of athletes. \(^3,5\) Two recent studies \(3,5\) have suggested that extreme levels of physical activity, including marathon running, are associated with increased CAC. However, data evaluating high-volume activity athletes with known CAC and long-term clinical outcomes are scarce. Once CAC is discovered, a great clinical concern is whether continued high levels of activity accelerate the transition to clinical disease, including nonfatal and fatal CVD events. In the present study, although highly active men had slightly greater risk of CAC of at least 100 AU, a corresponding greater mortality was not seen.

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of physical activity associated with endurance athletes for whom the question of training-induced coronary calcification has been raised. Indeed, the key question addressed in the present study was whether the presence of high CAC associated with high levels of exercise training as typically practiced by masters marathon runners is associated with greater mortality. For this question, the answer is clearly no.

**Strengths and Limitations**

Strengths of this study include the large sample (21,758 men), long mean duration of follow-up (10.4 years), and the availability of self-reported and measured risk factor information for risk estimation and multivariate analyses. The overall risk profile would suggest that sufficient risk exists within the population for the outcomes of interest to occur. Although physical activity is self-reported, the extensive questionnaire allows solid definition of total physical activity volume. An ample subcohort also underwent treadmill exercise testing for CRF assessment and demonstrated a strong association between reported high levels of activity and high CRF, supporting the cogency of self-reported activity levels.

Limitations in this study include the homogeneity of the population that is predominantly white, well educated, and with access to health care. Although limiting generalizability, this homogeneity removes unmeasured confounders and emphasizes the exposures of interest, including physical activity and CAC. The cross-sectional nature of the analysis between physical activity and CAC limits our ability to make a direct causal inference, but results are suggestive of the physical activity and CAC association previously described. The selected covariates were based on the Framingham Cardiovascular Risk equation and represent consistently available variables. Although data regarding baseline statin use are available, information on the length of use or the chronic lipid control level is not. Further, multiple visits were not analyzed owing to the limited mortal events in those with more than 1 visit and, hence, lack information on whether CAC discovery might have led to lifestyle and/or treatment modification. Thus, the patients’ rationale for their high levels of activity is unknown (eg, influence of risk status or existing medical problems).

In this large cohort with long duration of follow-up and a focus on the tail of a distribution, statistical power is limited. Of the 759 deaths, only 40 are among those with high physical activity levels. Power to detect all-cause mortality HRs to 1.60 for high vs low physical activity levels falls below 80% among those with CAC of at least 100 AU as well as less than 100 AU. Power to detect CVD mortality HRs to 2.00 among those with CAC of at least 100 AU and to 2.50 among those with CAC of less than 100 AU falls below 80%. Consequently, and although all our evidence suggests diminished risk at high levels of physical activity, we are unable to rule out risk ratios to these limits.

**Conclusions**

The present study, with, what is to our knowledge, the best available mortality data in a large population with CAC and quantification of physical activity, advances our understanding of the association of high levels of physical activity, clinically relevant CAC, and mortality. An 11% increase occurred in the adjusted prevalence of CAC of at least 100 AU in the most highly active group, most of whom had a CAC of less than 100 AU. In the presence of CAC and high levels of physical activity, however, the risk of all-cause and CVD mortality was less (compared with lower levels of physical activity) and thus appears to provide evidence against the hypothesis that high levels of activity increase the risk of all-cause or CVD mortality. Our findings should reassure patients and their health care professionals that it appears these highly active individuals can safely continue their exercise programs.
Association of Mortality With High Levels of Physical Activity and Coronary Artery Calcification


