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Coronary artery calcium and physical performance as determinants of mortality in older age: the AGES-Reykjavik Study

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ABSTRACT

Background Coronary artery calcium (CAC) and physical performance have been shown to be associated with mortality, but it is not clear whether one of them modifies the association. We investigated the association between the extent of CAC and physical performance among older individuals and explored these individual and combined effects on cardiovascular disease (CVD) and non-CVD mortality.

Methods We studied 4074 participants of the AGES-Reykjavik Study who were free from coronary heart disease, had a CAC score calculated from computed tomography scans and had data on mobility limitations and gait speed at baseline in 2002-2006 at a mean age of 76 years. Register-based mortality was available until 2009.

Results Odds for mobility limitation and slow gait increased according to the extent of CAC. Altogether 645 persons died during the follow-up. High CAC, mobility limitation and slow gait were independent predictors of CVD and non-CVD mortality. The joint effect of CAC and gait speed on non-CVD mortality was synergistic, i.e. compared to those with low CAC and normal gait, the joint effect of high CAC and slow gait exceeded the additive effect of these individual exposures on non-CVD mortality. For CVD mortality, the effect was additive i.e. the joint effect of high CAC and slow gait did not exceed the sum of the individual exposures.

Conclusions The extent of CAC and decreased physical performance were independent predictors of mortality and the joint presence of these risk factors increased the risk of non-CVD mortality above and beyond the individual effects.

INTRODUCTION

The extent of coronary artery calcium (CAC) is strongly correlated with the lifetime burden of atherosclerosis in the coronary arteries [1,2] and it has been shown to capture the cumulative exposure to cardiovascular risk factors in the older population [3-5]. Although CAC is a common finding in older individuals who have a high cardiovascular disease (CVD) risk profile, high CAC scores have also been reported among older persons with no CVD risk factors [4].

Some evidence exists on the association of subclinical measures of atherosclerosis such as carotid plaques and higher common carotid artery intima-media thickness [6] and higher levels of CAC [7-9] with slower gait speed. The extent of CAC [10-12,5,13] and decreased physical performance [14-17] have been shown to predict cardiac events and all-cause and CVD mortality in midlife and at older age. While increased CAC and decreased physical performance share similar health- and lifestyle-related risk factors, it is not clear if CAC and physical performance are independently associated with CVD and non-CVD mortality or whether one of them modifies this association. So far this combined association has not been studied in detail in an older representative population.

The purpose of this study was first to investigate the association between the extent of CAC and physical performance among older individuals with no prevalent coronary heart disease (CHD). Secondly, we explored the individual and combined effects of the extent of CAC and physical performance on CVD and non-CVD mortality in a well-characterized older population.

METHODS

Study population

The data come from the Age, Gene/Environment Susceptibility –Reykjavik Study (AGES-Reykjavik) conducted in 2002 to 2006 [18]. The 5764 individuals included in the AGES-Reykjavik Study were born between 1907 and 1935 and were randomly selected from the 11549 survivors of the Reykjavik Study cohort, which was initiated in 1967 by the Icelandic Heart Association [19]. From the AGES-Reykjavik sample of 5764 individuals, we excluded persons with a history of CHD (n=1209, 62.8% men) if they reported having a history of coronary artery disease or coronary artery bypass surgery or angioplasty or angina pectoris on the Rose Angina Questionnaire [20] or had evidence on electrocardiogram of possible or probable myocardial infarction. The analytical sample used in the analyses includes 4074 (37.2% men) individuals who had complete data on CAC, physical performance measurements and cause of death. Compared to the non-participants of the AGES-Reykjavik Study cohort (n=1690), the individuals in the analytical sample were younger (t-test $p<0.001$), more frequently non-smokers and had less diabetes or hypertension ($\chi 2$ tests $p< 0.001$). The National Bioethics Committee in Iceland (VSN:00-063) and the Institutional Review Board of the Intramural Research Program of the National Institute on Aging and the Data Protection Authority in Iceland approved the study. Informed consent was obtained from all participants.

Coronary artery calcium

A Siemens Somatom Sensation 4 multidetector computed tomography (CT) (Siemens Medical Solutions) with prospective electrocardiographic triggering was used to image the coronary arteries at baseline [18]. Calcium scoring software described by the Multi-Ethnic Study of Atherosclerosis study [21] was used to analyze the CT scans. Agatston score [22] was calculated

as the sum of 4 major coronary artery scores to quantify the extent of CAC. The intrareader agreement and the intraobserver correlation were found to be high in the AGES-Reykjavik Study sample [23].

Physical performance

Physical performance was assessed with standardized measures on perceived mobility ability and usual gait speed [24]. Both gait speed and perceived mobility ability have been found to be valid indicators of mobility limitation in an older population [25] as well as have high predictive validity for future disability, long-term care and mortality [14,24,26]. Participants were asked 'Because of health or physical problems do you have any difficulty walking 500 meters by yourself or without the use of aids?' and 'Do you have any difficulty walking up 10 steps without resting when you are by yourself and without the use of aids?' The answering alternatives were no difficulty, some difficulty, much difficulty and unable to do it because of health or physical reasons. As part of the clinical assessment, gait speed was measured over a 6-meter distance. Participants were asked to walk at their usual walking pace and the faster of two performances was used for each participant. Gait speed was calculated by dividing the distance with the walking time expressed in meters per second (m/s).

Mortality

Data on cause-specific mortality was collected from the national mortality register of Iceland. Survival time was calculated as the number of days between baseline in 2002-2006 and death or end of the follow-up in 2009, whichever happened first. Deaths caused by CVD, CHD, myocardial infarction, heart failure and stroke were included in the CVD mortality outcome (International Classification of diseases 10, ICD-10, codes I00-I99). All other causes of death

were included in the non-CVD mortality outcome (all other ICD-10 codes).

Covariates

Analyses were adjusted for demographics, lifestyle and chronic conditions and additionally for cognitive functioning, as these variables are associated with both CAC and physical performance [27]. Educational attainment was assessed as college/university vs. primary/secondary school and smoking history as never smoked vs. former or current smoker. Physical activity was assessed as the self-reported level of physical activity during the life course, categorized as moderate or high level vs. occasionally physically active at most. Body mass index (BMI), calculated as weight (kg) divided by height (m) squared, and total serum cholesterol, reported in mmol/l, were measured at the clinical assessment. The presence of diabetes was determined as having a history of diabetes, using glucose-modifying medication or fasting glucose of >7 mmol/l and hypertension as measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported history of hypertension or a history of using antihypertensive medication. Other chronic conditions included prevalence of arthritis and chronic obstructive pulmonary disease (COPD). The number of correct cells in the Digit Symbol Substitution Test (DSST) was used to assess cognitive functioning [28], because it has been suggested to modify the effect of subclinical atherosclerosis and physical performance [6].

Statistical analyses

Because of the exclusion of individuals with a history of CHD and high gender differences in coronary artery calcium, the CAC scores were divided into gender-specific quartiles with distribution-based cut-offs of <95.40, 95.40-389.81, 389.82-1039.35 and >1039.35 for men and

<9.45, 9.45-115.27, 115.28-444.23 and >444.23 for women. Perceived mobility ability was dichotomized into mobility limitations (at least some difficulties in walking 500 meters and/or climbing 10 steps) and no limitation (no difficulties in walking 500 meters and climbing 10 steps). Measured gait speed was dichotomized into slow gait speed (<0.8 m/s) and normal gait speed (≥0.8 m/s) [29,17]. To test for potential gender differences we first analyzed the interaction 'gender*CAC' on physical performance in a logistic regression model and then the interaction 'gender*CAC*physical performance' on CVD and non-CVD mortality in a Cox regression, but because these terms were non-significant (all p-values >0.275), subsequent analyses were pooled by gender.

Baseline characteristics of the participants were tested across the CAC quartiles using $\chi 2$ test for categorical variables and analysis of variance for continuous variables. The bivariate age-adjusted differences were compared for dichotomized variables using logistic regression and for continuous variables using the analysis of covariance. The associations between CAC and physical performance measures were analyzed with multivariate logistic regression models. For further analyses, the CAC score quartiles were dichotomized into the 4th quartile (indicating high CAC) vs. the 1st through 3rd quartiles (indicating low CAC). The extent of CAC and physical performance was examined as independent risk factors for CVD and non-CVD mortality with Cox proportional hazards models. The proportional hazards assumption was tested with the Cox time-dependent regression to identify variables for which associations were moderated by the time elapsed between the survey and death. Second, we investigated the individual and combined effects of CAC and physical performance on CVD and non-CVD mortality. The synergistic interactions were evaluated as departure from additivity for CAC and physical performance on CVD and non-CVD mortality reporting the synergy index (SI) and the 95%

confidence interval [30,31]. The synergy index is equal to the calculation of [HR11 – 1] / [HR10 – 1) + (HR01 – 1)], where HR10 denotes exposure to one and HR01 to the other risk factor and HR11 to both risk factors. A synergistic interaction is defined to be present if SI > 1 [30], indicating that the joint effect of the two exposures is greater than the sum of the individual effects of the two exposures. Mortality rates per 1000 person-years and 95% confidence intervals according to CAC and physical performance were calculated for the follow-up time. All analyses were first adjusted for age and gender and then for education, smoking, physical activity, BMI, total cholesterol and prevalent diabetes, hypertension, arthritis and COPD.

RESULTS

Mean age of the participants at baseline was 76.3 years (standard deviation 5.5) and 37.2% were men. Table 1 presents bivariate associations for baseline characteristics across the CAC quartiles. There was a strong positive association with older age and higher level of CAC. The proportion of individuals with mobility limitation increased significantly across the CAC quartiles and gait speed was slower according to a higher degree of CAC. The prevalence of diabetes, hypertension and COPD increased significantly across the CAC quartiles.

Coronary artery calcium and physical performance

The odds for mobility limitation and slow gait speed increased according to the extent of CAC, presented in Table 2. Adjustment for education, lifestyle and health factors attenuated these associations only slightly. We further adjusted for cognitive functioning with the DSST score, but the results did not materially change.

Individual and combined effects of CAC and physical performance on mortality

Mean length of follow-up for the 4074 individuals was 5.4 years (range 0.2-7.6), during which 645 (15.8%) persons died. Of the deaths, 267 were caused by CVD and 378 by non-CVD of which 223 deaths were caused by cancer or benign tumor at any site and 155 of other causes such as Alzheimer's disease and pneumonia. A high level of CAC compared to low CAC increased the risk for CVD and non-CVD mortality in the fully adjusted proportional hazards model, presented in Table 3 (Model 2). Similarly, mobility limitation compared to no limitations and slow gait speed compared to normal gait speed independently predicted CVD and non-CVD mortality during the follow-up period. Multiple adjustments and further adjustment for cognition had little effect on these associations.

We studied the combined effect of CAC and physical performance on CVD and non-CVD mortality and interactions were examined using the Rothmans Synergy Index (SI), presented in Table 3. The findings were similar for CAC and both physical performance measures and are thus presented only for CAC and gait speed in Figure 1. The interaction between CAC and gait speed on CVD and non-CVD mortality was synergistic, indicated by a SI > 1, but significant only for CAC and gait speed on non-CVD mortality, SI 6.51 95% confidence interval (CI) 1.06-39.82. In the combined model, having only one of the exposures, i.e. either a high level of CAC or slow gait speed, was not statistically significantly associated with non-CVD mortality compared to those with low CAC and normal gait (referent), HR 1.23 95% CI 0.94-1.62 and 1.08 95% CI 0.78-1.50, respectively. However, the risk of dying from non-CVD causes during the follow-up for those with both high CAC and slow gait exceeded the sum of the individual risks of the two exposures compared to the referent, HR 2.75 95% CI 2.03-3.71. In terms of CVD mortality, the effect was additive. Compared to those with low CAC and normal gait speed, the individuals with one of these exposures had a two-fold risk of CVD death whereas the hazard ratio was 3.48 95% CI 2.41-5.02 for those with both high CAC and slow gait. Similar associations for CAC and gait speed were observed for mortality rates per 1000 person-years for CVD and non-CVD mortality, presented in Table 4 and in the Kaplan-Meyer survival curves, presented in Figure 2. Adjustment for education, lifestyle factors, chronic diseases such as diabetes and hypertension and, additionally, for cognitive functioning had little effect on the findings. Furthermore, we tested whether other co-morbidities such as diabetes mediated the association, but the results were similar in the analyses confined to the non-diabetics.

DISCUSSION

In this large population-based cohort of older people free from coronary heart disease, we found the extent of coronary artery calcium, a marker of the lifetime accumulation of subclinical coronary atherosclerosis, to be associated with physical performance. In addition to CAC and physical performance being independent predictors of CVD and non-CVD mortality, we identified a positive synergistic interaction between the extent of CAC and gait speed on non-CVD mortality, which was above and beyond the individual effects of these risk factors. These associations were independent of socio-demographics, several lifestyle and health factors and cognitive functioning.

The present results parallel earlier cross-sectional findings on the inverse relation between a higher level of CAC and slower gait speed, which have been reported in older adults free from cardiovascular disease [7-9]. The cross-sectional nature of our analyses refrain us from making assumptions on the causal nature of the relation between coronary calcium and physical performance. However, atherosclerosis is a slowly progressing disease that infiltrates the arterial wall well before symptoms appear and might originate in as early as infancy [33,34]. Subclinical coronary atherosclerosis might play a role in physical performance, with impaired gait reflecting the consequences of underlying pathophysiological processes such as inflammation and altered hemodynamic and metabolic control [35,36]. It has been suggested that inflammation (associated with subclinical coronary atherosclerosis) would accelerate skeletal muscle atrophy and subsequently decrease physical performance [37,38]. Other important mechanisms might also explain the association between CAC and physical performance, e.g. peripheral arterial disease, indicating subclinical atherosclerosis, might have led to decreased performance among these older individuals [39]. On the other hand, the

relationship between CAC and gait might also be reversed, i.e. the beneficial effects of physical fitness indicated by intact physical performance might slow down the development of CAC and thus be an antecedent rather than a consequence of coronary atherosclerosis. However, findings on the association of physical activity and CAC have been rather weak and inconsistent [40,8].

In line with previous findings, our results showed that the level of CAC and both physical performance measures were independent predictors of CVD mortality [10,11,15] and non-CVD mortality [12,16,17]. We found an additive effect of CAC and physical performance on CVD-mortality, showing that they were both independently associated with the outcome, but that the combined effect of these exposures did not exceed the sum of the individual effects. It might be that cardiovascular risk factors acting throughout life contributed equally to both high CAC and slow gait [5,15] and thus the combined effect did not yield any further risk in terms of fatal CVD events. In terms of non-CVD mortality, exposure to both risk factors, high CAC and slow gait, increased the risk above and beyond the individual effects.

It is likely that there are several mechanisms explaining the synergistic effect of CAC and gait on non-CVD mortality. First, chronic inflammation may be what is driving the additive cumulating effect of CAC and gait on mortality which is above and beyond the separate effects of these exposures. Chronic inflammation has been shown to be present in subclinical atherosclerosis [34] as well as to be associated with muscle atrophy and lower physical functioning [36]. The presence of both high CAC and slow gait might exacerbate the subsequent risk of mortality. Inflammation might also serve as an indicator of another disease process involving inflammation such as cancer [41,42] and dementia [43,23] which further increases the risk of

death. Second, the synergistic interaction could be explained by disease severity in that CAC and gait would simply be indicators of pending death. However, length of follow-up was similar among those who died of CVD and non-CVD causes. Third, it is also possible that other co-morbidities such as diabetes mediated the association. However, adjusting for diabetes and further excluding those with prevalent diabetes yielded similar results.

Study strengths and limitations

The strength of our study lays in the well-characterized population-based study sample. Cardiac imaging with the multidetector CT scan in measuring coronary artery calcium has been shown to be a valid measure of coronary atherosclerosis [44]. We used both subjective and objective measures of physical performance with valid cut-offs that have been shown to predict subsequent disability, long-term care and mortality [14,24,26]. The cause-specific data on mortality was collected from the national mortality register of Iceland. Some limitations of the study should be recognized. We did not use absolute cut-offs for CAC, as recommended by e.g. Budoff et al. [45], due to the exclusion of individuals with a history of CHD. This should also be noted when generalizing these results. The study population consisted of survivors of the Reykjavik Study who were on average 76 years of age, which might cause some underestimation in terms of the results, while both higher level of CAC and decreased physical performance increase the risk for mortality [12,16] causing those less healthy to drop out of the study sample. We did not have data on the events and health status prior to death for the majority of the participants. It might be that among those who died of CVD or non-CVD causes, there were differences in the number that had been diagnosed with CHD and received treatment for the condition between the time of the baseline and death that altered the mortality risk for those with combined exposure.

Conclusions

In this older cohort, the extent of CAC and decreased physical performance were independent predictors of mortality. The combined effect of these risk factors was additive for CVD mortality indicating that the presence of both risk factors did not yield any further risk in terms of fatal CVD events. However, the combined presence of these risk factors increased the risk of non-CVD mortality above and beyond the individual effects indicating that these individuals might have a particularly high risk for adverse health events warranting further investigation. Assessing vitality of older people with a physical performance measure such as gait speed is easy to implement in public health care [17], whereas measuring coronary artery calcium with a CT scan on population level is unrealistic [46]. The present findings suggest that a simple physical performance measure such as gait speed could help to identify those, who might have prevalent, but clinically still silent atherosclerosis. These individuals might potentially benefit from further assessment of the risk of subclinical coronary atherosclerosis while the present findings indicate that the risk of adverse health events is clearly higher among these older individuals.

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Legends for Figures:

Figure 1

Age- and gender-adjusted hazard ratios and 95% confidence intervals for CVD and non-CVD mortality according to coronary artery calcium (CAC) and gait speed

Figure 2

Survival curves for CVD and non-CVD mortality according to coronary artery calcium (CAC) and gait speed

Table 1 Baseline characteristics according to the extent of coronary artery calcium among individuals with non-prevalent coronary heart disease in the AGES-Reykjavik Study, n=4074

	Coronary artery calcium quartiles*				
Characteristics	**1st**	**2nd**	**3rd**	**4th**	**p†**
Men, n (%)	381 (36.9)	381 (37.1)	380 (37.2)	374 (37.7)	-
Age, mean (SD)	74.3 (4.9)	75.7 (5.4)	76.8 (5.4)	78.4 (5.7)	<0.001
No mobility limitations, n (%)					
Men	315 (82.7)	296 (77.7)	286 (75.3)	249 (66.6)	<0.001
Women	472 (72.5)	421 (65.1)	377 (58.8)	336 (53.6)	<0.001
Gait speed m/s, mean (SD)					
Men	1.06 (0.2)	1.03 (0.2)	1.01 (0.2)	0.96 (0.2)	<0.001
Women	1.01 (0.2)	0.97 (0.2)	0.94(0.2)	0.89 (0.2)	<0.001
Gait speed <0.8 m/s, n (%)					
Men	37 (9.7)	47 (12.3)	67 (17.6)	86 (23.0)	0.001
Women	79 (12.1)	129 (19.9)	159 (24.8)	213 (34.4)	<0.001
BMI, mean (SD)					
Men	26.53 (3.8)	26.32 (3.9)	26.76 (3.6)	27.27 (3.9)	<0.001
Women	27.30 (4.6)	27.40 (4.9)	26.92 (4.9)	27.05 (4.8)	0.42
Cholesterol mmol/l, mean (SD)	5.80 (1.0)	5.90 (1.1)	5.85 (1.1)	5.79 (1.1)	0.063
DSST score, median (SE)	32.0 (2.4)	29.0 (2.4)	29.0 (3.0)	25.0 (2.0)	0.032
University/college education, n (%)	289 (28.0)	288 (28.0)	280 (27.5)	256 (25.8)	0.34
Never smoked, n (%)	555 (53.8)	472 (45.9)	427 (41.9)	411 (41.4)	<0.001
Moderate/vigorous physical activity during lifetime, n (%)	327 (34.2)	306 (32.0)	322 (33.9)	271 (29.3)	0.70
Prevalent chronic diseases, n (%)					

Diabetes	85 (8.2)	105 (10.2)	123 (12.0)	130 (13.1)	<0.001
Hypertension	719 (69.7)	784 (76.3)	813 (79.6)	821 (82.7)	<0.001
Arthritis	401 (39.7)	407 (40.3)	372 (37.0)	392 (40.5)	0.88
COPD	81 (7.8)	77 (7.5)	85 (8.3)	80 (8.1)	0.67

BMI= Body mass index, COPD= Chronic obstructive pulmonary disease, DSST= Digit Symbol Substitution Test

*Gender-specific

†Age-adjusted p value for overall difference between quartiles

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) for mobility limitation and slow gait speed according to the extent of coronary artery calcium (CAC) among individuals with non-prevalent coronary heart disease in the AGES-Reykjavik Study, n=4074

	Mobility limitation*		**Slow gait speed†**	
	Model 1	**Model 2**	**Model 1**	**Model 2**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
CAC				
1st quartile	1.00	1.00	1.00	1.00
2nd quartile	1.28 (1.05 - 1.57)	1.16 (0.93 - 1.45)	1.35 (1.04 - 1.75)	1.26 (0.95 - 1.66)
3rd quartile	1.51 (1.24 - 1.84)	1.45 (1.16 - 1.80)	1.65 (1.28 - 2.13)	1.48 (1.13 - 1.95)
4th quartile	1.82 (1.49 - 2.23)	1.63 (1.30 - 2.03)	2.09 (1.63 - 2.68)	1.84 (1.40 - 2.41)
P value‡	<0.001	<0.001	<0.001	<0.001

*Mobility limitation= at least some limitation vs. no limitations in self-reported ability to walk 500 meter and climb up 10 steps.

†Slow gait speed=slow gait speed <0.8 m/s vs. normal gait speed ≥0.8 m/s.

‡Wald test across the CAC categories.

Model 1 adjusted for age and gender.

Model 2 adjusted for age, gender, education, smoking, physical activity, body mass index, total cholesterol, prevalent hypertension, diabetes, arthritis and chronic obstructive pulmonary disease.

Table 3 Hazard ratios (HR) and 95% confidence intervals (CI) for cardiovascular and non-cardiovascular mortality according to the extent of coronary artery calcium (CAC), perceived mobility and gait speed among individuals with non-prevalent coronary heart disease in the AGES-Reykjavik Study, n=4074

	Cardiovascular disease mortality			**Non-cardiovascular disease mortality**		
	Deaths/ group	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Deaths/ group**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**
Coronary artery calcium						
Low CAC	148/2841	1.00	1.00	240/2933	1.00	1.00
High CAC	119/855	1.85 (1.44 - 2.37)	1.89 (1.46 - 2.46)	138/874	1.63 (1.32 - 2.00)	1.60 (1.28 - 2.01)
Perceived mobility						
No limitations	127/2535	1.00	1.00	213/2621	1.00	1.00
At least some limitations	140/1161	1.97 (1.53 - 2.52)	2.01 (1.53 - 2.65)	165/1186	1.71 (1.39 - 2.09)	1.90 (1.51 - 2.39)
Gait speed						
Normal gait speed	152/2995	1.00	1.00	262/3105	1.00	1.00
Slow gait speed	115/701	1.99 (1.53 - 2.59)	1.89 (1.43 - 2.50)	116/702	1.53 (1.21 - 1.94)	1.56 (1.21 - 2.00)
CAC & perceived mobility						

Synergy Index	1.38 (0.78 – 2.45)	2.93 (1.12 – 7.66)
CAC & gait speed		
Synergy Index	1.24 (0.69 – 2.23)	6.51 (1.06 – 39.82)

CAC dichotomized into 4th quartile (high CAC) vs. 1st to 3rd quartile (low CAC), mobility ability into at least some difficulties (limitation) vs. no difficulties (no limitation), gait speed into <0.8 m/s (slow gait) vs. ≥0.8 m/s (normal gait).

Model 1 adjusted for age and gender.

Model 2 adjusted for age, gender, education, smoking, physical activity, body mass index, total cholesterol, prevalent hypertension, diabetes, arthritis and chronic obstructive pulmonary disease.

Table 4 Unadjusted mortality rates per 1000 person-years and 95% confidence intervals (CI) according to CAC and gait speed among individuals with non-prevalent coronary heart disease

	Cardiovascular mortality rate (95% CI)				**Non-cardiovascular mortality rate (95% CI)**			
Gait speed	**no CAC**		**CAC**		**no CAC**		**CAC**	
High	6.5	(5.2 - 7.9)	18.5	(14.4 - 23.3)	13.8	(11.8 - 15.9)	20.5	(15.9 - 25.7)
Low	23.7	(18.1 - 30.4)	45.6	(34.0 - 58.9)	19.6	(14.4 - 25.6)	54.6	(42.3 - 68.4)
p value[a]	<0.001				<0.001			

[a]Log-Rank test.

Figure 1

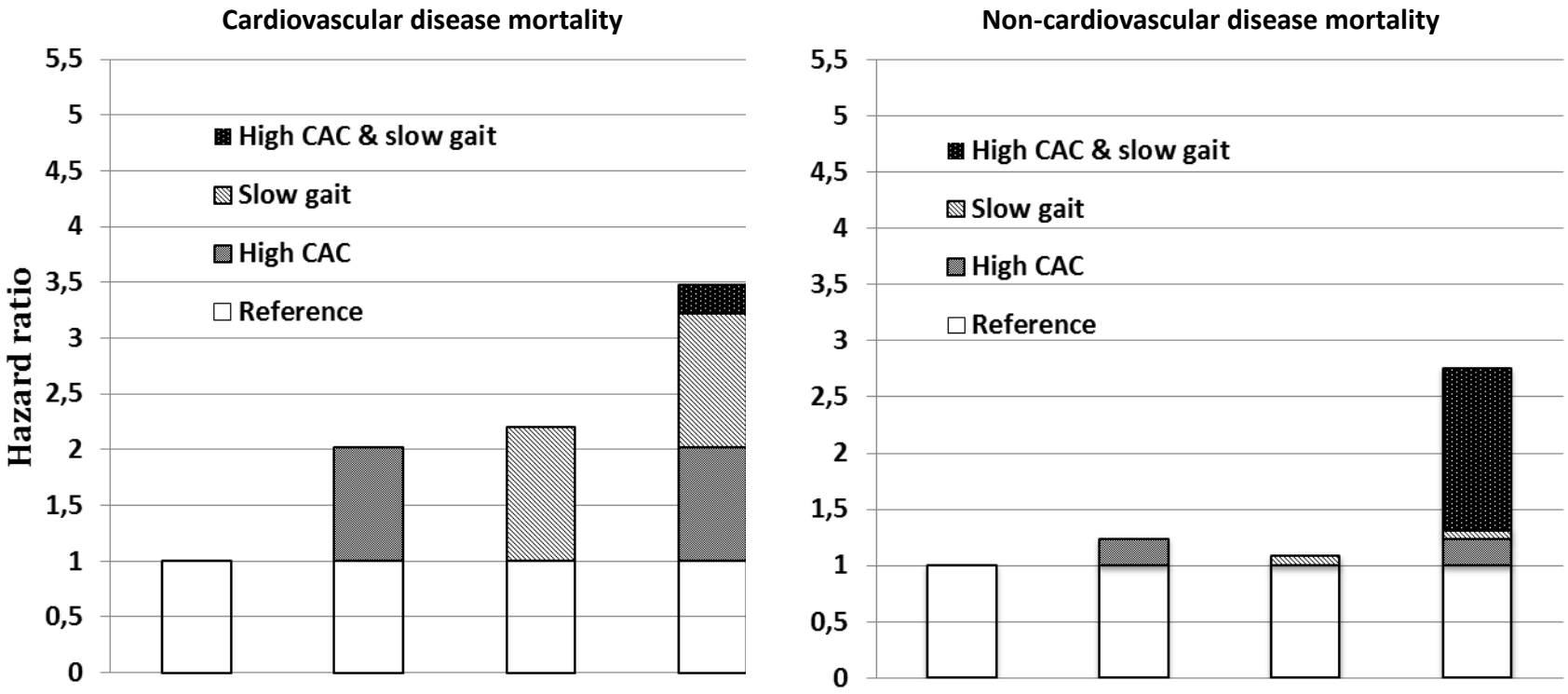
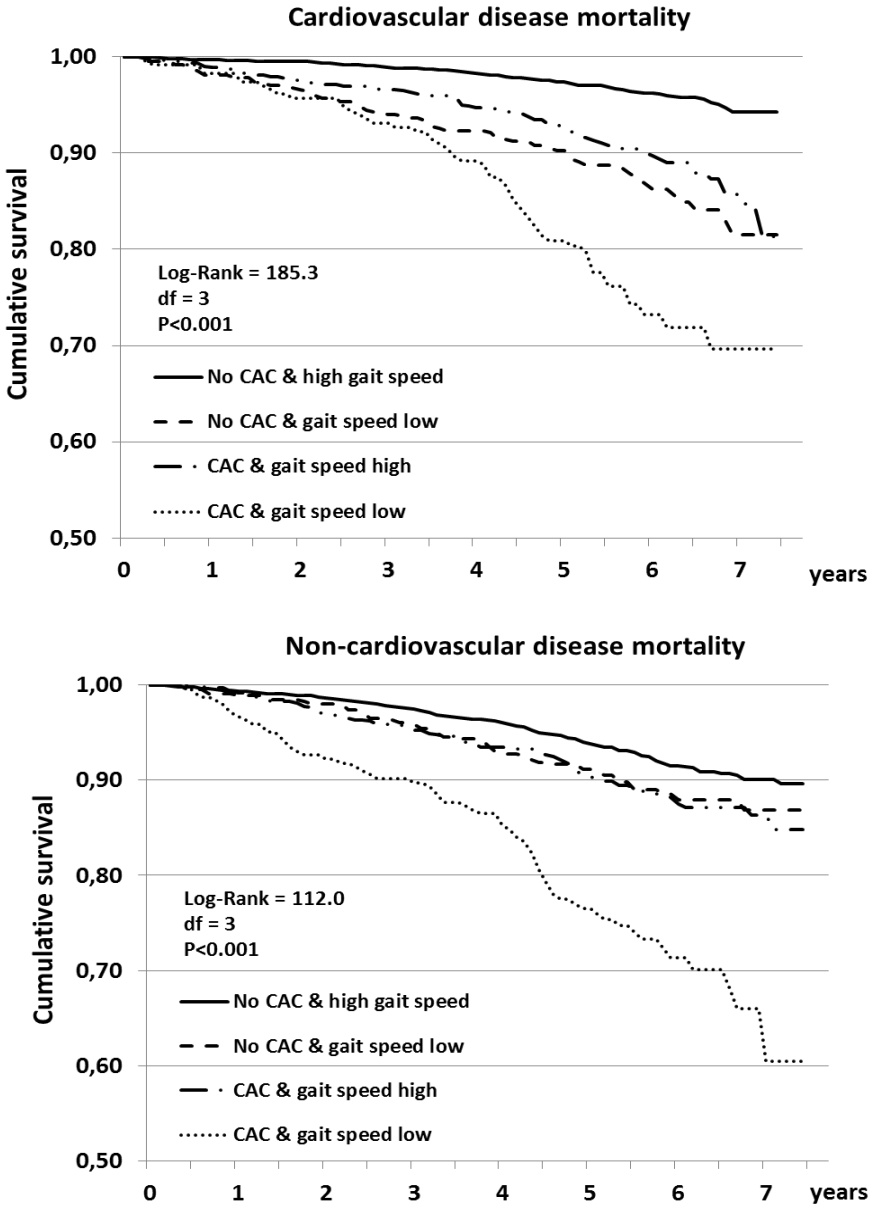

Cardiovascular disease mortality
Hazard ratio
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
High CAC & slow gait
Slow gait
High CAC
Reference
Non-cardiovascular disease mortality
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
High CAC & slow gait
Slow gait
High CAC
Reference

Figure 2


Cardiovascular disease mortality
Cumulative survival
1,00
0,90
0,80
0,70
0,60
0,50
Log-Rank = 185.3
df = 3
P<0.001
No CAC & high gait speed
No CAC & gait speed low
CAC & gait speed high
CAC & gait speed low
0
1
2
3
4
5
6
7
years
Non-cardiovascular disease mortality
Cumulative survival
1,00
0,90
0,80
0,70
0,60
0,50
Log-Rank = 112.0
df = 3
P<0.001
No CAC & high gait speed
No CAC & gait speed low
CAC & gait speed high
CAC & gait speed low
0
1
2
3
4
5
6
7
years