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ORIGINAL RESEARCH

Coronary Artery Calcium and Cognitive Function in Dutch Adults: Cross-Sectional Results of the Population-Based ImaLife Study

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BACKGROUND: The aim of this study was to investigate whether increased severity of coronary artery calcium (CAC), an imaging biomarker of subclinical coronary atherosclerosis, is associated with worse cognitive function independent of cardiovascular risk factors in a large population-based Dutch cohort with broad age range.

METHODS AND RESULTS: A cross-sectional analysis was performed in 4988 ImaLife participants (aged 45–91 years, 58.3% women) without history of cardiovascular disease. CAC scores were obtained using nonenhanced cardiac computed tomography scanning. The CogState Brief Battery was used to assess 4 cognitive domains: processing speed, attention, working memory, and visual learning based on detection task, identification task, 1-back task, and 1-card-learning task, respectively. Differences in mean scores of each cognitive domain were compared among 4 CAC categories (0, 1–99, 100–399, ≥400) using analysis of covariates to adjust for classical cardiovascular risk factors. Age-stratified analysis (45–54, 55–64, and ≥65 years) was performed to assess whether the association of CAC severity with cognitive function differed by age. Overall, higher CAC was associated with worse performance on 1-back task after adjusting for classical cardiovascular risk factors, but CAC was not associated with the other cognitive tasks. Age-stratified analyses revealed that the association of CAC severity with working memory persisted in participants aged 45 to 54 years, while in the elderly this association lost significance.

CONCLUSIONS: In this Dutch population of ≥45 years, increased CAC severity was associated with worse performance of working memory, independent of classical cardiovascular risk factors. The inverse relationship of CAC score categories with working memory was strongest in participants aged 45 to 54 years.

Key Words: atherosclerosis ■ cognitive function ■ coronary artery calcium ■ dementia

The number of people with cognitive impairment and dementia is increasing worldwide because of growing older populations, and this has become a public health concern.[1] Typically, there is a long preclinical stage before clinical symptoms of dementia become apparent.[2,3] This long time window offers the opportunity to investigate potential biomarkers that can identify individuals who are at risk of (early) cognitive changes, and subsequently, potential interventions can be applied in an early stage that may prevent or delay the cognitive decline. It has been shown that cardiovascular risk factors, such as smoking, hypercholesterolemia, hypertension, and obesity contribute to cognitive impairment and dementia.[4] Coronary artery calcium (CAC), an imaging biomarker of atherosclerosis burden, reflects

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CLINICAL PERSPECTIVE

What Is New?

- In a Dutch population of individuals ≥45 years, increased coronary artery calcium severity was associated with worse performance of working memory, independent of classical cardiovascular risk factors.
- The inverse relationship of coronary artery calcium score categories with working memory was strongest in individuals aged 45 to 54 years.

What Are the Clinical Implications?

- Coronary artery calcium scoring may be useful to identify individuals at elevated risk of cognitive dysfunction and dementia.

Nonstandard Abbreviations and Acronyms

DET	detection task
IDN	identification task
OBK	1-back task
OCL	1-card-learning task

the effect of lifetime exposure to cardiovascular risk factors on the coronary arterial wall, and provides added value in predicting cardiovascular events.[5] Thus, there may be a potential role for CAC to predict early cognitive decline and dementia. Prior studies have investigated the association between CAC and risk of dementia and cognitive decline, but results were inconsistent and with limited evidence supporting a significant inverse association.[6–11]

Besides the aforementioned modifiable cardiovascular risk factors, chronological age is inversely associated with cognitive performance. Evident cognitive decline can start from the age of 45 years.[12] The available evidence on associations between CAC and cognitive function at a relatively young age is limited.[10,13] However, knowledge about whether subclinical atherosclerosis is involved in early cognitive decline at a young age is important because this could offer the opportunity to intervene and reduce or halt atherosclerosis burden at middle-life, and may prevent or slow down cognitive decline in later life.[10,14] Therefore, further research is needed to investigate the relation between subclinical atherosclerosis and cognitive function, not only in elderly but also in younger adults.

The ImaLife study, embedded in the Dutch population-based Lifelines cohort, with comprehensive data collection of classical cardiovascular risk factors, nonenhanced cardiac computed tomography (CT) scans for CAC assessment, and validated cognitive testing based on a fast computerized tool, allows investigation of the association between CAC and cognitive function in a broad age group.[15,16] We examined the hypothesis that increased CAC severity is associated with worse cognitive function independently of classical cardiovascular risk factors. We further examined whether the association differed by age groups.

METHODS

For access to the data that support the findings of this study, the Lifelines research office can be contacted via www.lifelines.nl/researcher.

Study Set-Up and Population

The Lifelines study, a population-based cohort study in the northern Netherlands, was launched in 2006 (baseline round) to investigate environmental, genetic, behavioral, physical, and psychological factors that may contribute to health and disease.[15] In general, participants complete questionnaires every 1.5 years and revisit for examinations every 5 years. Data collection of the Lifelines cohort includes assessment of demographic and classical cardiovascular risk factors, as well as blood pressure measurements, blood laboratory tests, and cognitive function testing. The ImaLife study, embedded in the Lifelines cohort, was initiated in August 2017 to establish reference values of imaging biomarkers for early stages of coronary artery disease, lung cancer, and chronic obstructive pulmonary disease, as described in the study design article.[16] All Lifelines subjects (aged ≥45 years) who were eligible for the ImaLife study were invited for a CT examination of heart and lungs. The ImaLife study was approved by the medical ethics committee of the University Medical Center Groningen, The Netherlands. Informed consent was given by all participants. For the current study, a shifted time cross-sectional study design was used. We included 5162 participants who have completed cognitive function testing during the second round assessment (2014–2017) and had undergone cardiac CT scanning (2017–March 2020). In total, 174 participants were excluded; they either had a history of coronary heart disease (defined as self-reported history of myocardial infarction, and/or coronary artery bypass grafting or percutaneous coronary intervention, and/or signs of myocardial infarction on electrocardiography) and/or a self-reported history of stroke. A total of 4988 participants were included for the final analyses.

CAC Score

A low-dose nonenhanced cardiac CT scan was performed using a third-generation dual-source CT (Somatom Force, Siemens Healthineers, Germany).

The scan was performed with electrocardiographic triggering at 65% of the R-R interval. The scan covered the whole heart from carina to the apex. Tube voltage was 120 kVp and reference of tube current was 64 mAs per rotation. Images were reconstructed with a field of view of 250 mm, slice thickness of 3.0 mm, and increment of 1.5 mm, with filtered back-projection and medium-sharp reconstruction kernel (Qr36d). Images were analyzed by well-trained physician researchers (C.X. and R.M.) using commercial software (Syngo. via VB30A, CaScoring, Siemens). The Agatston score was used to quantify CAC.[17] CAC scores were stratified into 4 common categories: 0, 1 to 99, 100 to 399, and ≥400 (Figure).

Assessment of Cognitive Function

At the second round assessment of Lifelines, the CogState Brief Battery, a collection of computerized tests, was used to measure multiple core cognitive domains: processing speed, attention, working memory, and visual learning. Compared with cognitive tests used in other studies on the relation between CAC and cognitive function, the CogState Brief Battery is a computerized test that is less time- and labor intensive, which makes it well suited to evaluate cognitive functioning in large cohorts. The CogState Brief Battery has good test–retest reliability and is a feasible tool to detect subtle cognitive changes in preclinical states of a general population as well as cognitive impairment in clinical patients.[18–20] The CogState Brief Battery consisted of 4 tasks: (1) detection task (DET) measuring psychomotor function or speed of processing, (2) identification task (IDN) measuring visual attention, (3) 1-back task (OBK) measuring working memory, and (4) 1-card-learning task (OCL) measuring visual learning.[21] In the DET, participants were instructed by the on-screen question "Has the card turned over?". A face-down playing card was presented in the center of the screen; participants must react to flipping over of the card by pressing the button "yes" as soon as possible. The task ends after 35 correct responses have been recorded. In the IDN, participants were instructed by the on-screen question "Is the card red?". A face-down playing card was presented in the center of the screen. As soon as the playing card flips over, participants must decide whether the card is red or not by pressing the button "yes" or "no." The task ends after 30 correct responses. In the OBK, participants were instructed by the on-screen question "Is the previous card the same?". Participants must decide whether the face-up playing card is the same as the previous card or not by pressing the button "yes" or "no." The task ends after 30 correct responses. In the OCL, participants were instructed by the on-screen question "Have you seen this card before in this test?". Participants must decide whether they have seen the face-up playing card in this test or not by pressing the button "yes" or "no." The task continued until 80 trials had been completed. The primary outcome of DET and IDN was the speed of the performance that was expressed as mean reaction time (ms, log10 transformed for normalization) for correct responses. The primary outcome of OBK and OCL was the accuracy of performance, which is the proportion of correct answers (arcsine square root transformed for normalization). Lower scores for DET and IDN and higher scores for OBK and 1-card-learning task indicated better cognitive performance. More detailed information on the CogState Brief Battery can be found online (www.cogstate.com).

Other Covariates

Detailed information on cardiovascular risk factors was based on questionnaires, physical examination, and blood laboratory tests in the Lifelines cohort

Figure. Example of participants with different CAC score in each risk category.
Participant with a CAC score of 0 (**A**), CAC score of 34 (**B**), CAC score of 200 (**C**), and CAC score of 768 (**D**). CAC indicates coronary artery calcium.

at baseline and second round assessment. Use of medication was self-reported, and recorded using anatomical therapeutic chemical codes at baseline. To define cardiovascular risk factors, data from the most recent assessment were used, supplemented with data from prior assessments in case of missing information.

Smoking habits and level of education were assessed by self-report questionnaires. Smoking status was defined as current smoking or not by answering the question "do you smoke now or have you smoked in the past month?". Educational level was categorized as low (≤12 years) or high (>12 years) according to the international standard classification of education.[21,22] Blood pressure measurements, laboratory blood tests, and anthropometric measurements were conducted following standardized protocols, as reported previously.[15,23] Hypertension was defined as self-reported hypertension and/or systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medication. Hypercholesterolemia was defined as serum total cholesterol ≥6.2 mmol/L and/or use of lipid-lowering medication. Diabetes mellitus was defined as self-reported diabetes mellitus, and/or fasting glucose ≥7.0 mmol/L, and/or nonfasting glucose ≥11.1 mmol/L and/or glycated hemoglobin A1c ≥6.5% and/or use of oral antidiabetic medication or insulin. Body mass index was calculated as body weight divided by height squared (kg/m^2).

Statistical Analysis

Population characteristics were described using frequency or percentage for categorical variables, mean and SD, or median and interquartile range for continuous variables depending on the distribution. Differences by sex were evaluated using independent *t* test or Mann–Whitney *U* test where appropriate. ANCOVA was used to calculate mean scores and 95% CI of the 4 cognitive tasks for each CAC category. Given that the effect of CAC categories on 4 cognitive outcomes was tested, a Bonferroni adjusted *P* value of <0.0125 (0.05/4) was considered statistically significant. Model 1 included adjustment for age; model 2 included additional adjustment for sex and educational level; and model 3 included additional adjustment for current smoking, hypertension, hypercholesterolemia, diabetes mellitus, and body mass index. These models were used to investigate whether the association between CAC and cognitive function was independent of cardiovascular risk factors. Tukey's post hoc tests were conducted to determine which CAC categories differed in scores of each cognitive task. All analyses were further stratified by 45 to 54, 55 to 64, and ≥65 years age categories to investigate whether there was a modification effect of age. Sensitivity analyses were performed by generating an alternative model adjusted for systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol measured in the second round assessment (Table S1). A 2-tailed *P* value of <0.05 was set as significance level, except for ANCOVA. R (Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

RESULTS

Characteristics of the population are described in Table 1. Of the 4988 participants, 58.3% were female. Mean age was 57.4±8.4 years, ranging from 45 to 91 years. CAC was present in 47.9% of participants (63.8% of men and 36.6% of women). Median CAC score was higher in men (median 8, interquartile range 124) than in women (median 0, interquartile range 10, *P*<0.001). In participants with positive CAC, median CAC score was higher in men (median 62, interquartile range 262) than in women (median

Table 1. Characteristics of the Study Population (n=4988)

Characteristics	All
Age, y	57.4±8.4
Age, %	
45–54 y	40.6
55–64 y	39.3
≥65 y	20.1
Sex, female %	58.3
Race, White %	98.8
Educational levels, high %	30.4
Current smoking, yes %	15.1
SBP, mm Hg,	129.2±16.0
DBP, mm Hg	75.2±9.6
Hypertension, yes %	44.1
Total cholesterol, mmol/L	5.25±0.95
HDL cholesterol, mmol/L	1.59±0.43
LDL cholesterol, mmol/L	3.43±0.44
Hypercholesterolemia, yes %	25.7
Diabetes mellitus, yes %	5.0
Body mass index, kg/m^2	26.2±4.0
CAC score, AU %	
0	52.1
1–99	30.6
100–399	10.6
≥400	6.7

Values are number (percentage) or mean±SD. AU indicates Agatston units; CAC, coronary artery calcium; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SBP, systolic blood pressure.

33, interquartile range 108, $P<0.001$). Overall, the mean score of DET and IDN tests was 2.58±0.19 and 2.69±0.09, respectively. The mean score of OBK and OCL was 1.29±0.21 and 0.95±0.12, respectively. No differences of CogState subtasks were found by sex: DET (men 2.58±0.19, women 2.58±0.18, $P=0.77$), IDN (men 2.70±0.09, women 2.69±0.09, $P=0.29$), OBK (men 1.29±0.21, women 1.29±0.21, $P=0.59$), and OCL (men 0.95±0.12, women 0.95±0.12, $P=0.34$).

Table 2 shows the mean scores of DET, IDN, OBK, and OCL according to CAC categories, for the different models. In the age-adjusted analysis (model 1), significant differences in OBK scores were found across CAC categories, but not in DET, IDN, or OCL scores. This suggests that worse performances of working memory were associated with CAC severity, but psychomotor function, attention, and visual learning were not. Post hoc tests revealed significant differences between CAC ≥400 and CAC 0 for OBK scores. Adjustment for sex and educational level (model 2) did not substantially change overall differences in OBK. Further adjustment for cardiovascular risk factors (model 3) did not substantially change these results.

Table 3 shows the results of age-stratified analyses of associations among DET, IDN, OBK, and OCL scores and CAC categories. In participants aged 45 to 54 years, significant differences in OBK scores were observed across CAC categories, but not in DET, IDN, and OCL scores (model 1). Post hoc tests revealed that the OBK score in participants with CAC ≥400 was significantly lower than those with CAC 0, namely, 1.21 versus 1.33 ($P=0.002$). In multivariate models, the difference in OBK scores was slightly reduced but the relationship remained significant. Also in the older age categories, there was a trend towards lower OBK scores by CAC categories, but this did not reach statistical significance. In participants aged 55 to 64 years, there were small significant differences in IDN scores across CAC categories, but other scores did not differ significantly by CAC in multivariate models (model 3). Similarly, in participants aged ≥65 years, small differences in IDN scores across CAC categories were observed but not statistically significant.

Sensitivity analyses by alternating modeling adjustments to systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol showed similar results as adjustments for clinical determinations of disease phenotypes based on these conditions. Detailed information of sensitivity analysis can be found in Table S2.

DISCUSSION

In this population-based study of individuals aged ≥45 years without history of cardiovascular disease, cognitive performance of working memory showed

Table 2. Association of Severity of Coronary Artery Calcium With Cognitive Function Per Test

Cognitive tasks and Models	Coronary Artery Calcium Categories				*P* Value
	0	1–99	100–399	≥400	
Detection task					
Model 1	2.58 (2.57, 2.59)	2.58 (2.57, 2.59)	2.57 (2.56, 2.59)	2.58 (2.56, 2.60)	0.867
Model 2	2.58 (2.57, 2.59)	2.58 (2.57, 2.59)	2.57 (2.56, 2.59)	2.58 (2.56, 2.60)	0.821
Model 3	2.58 (2.57, 2.59)	2.58 (2.57, 2.59)	2.57 (2.56, 2.59)	2.58 (2.56, 2.60)	0.816
Identification task					
Model 1	2.69 (2.69, 2.70)	2.70 (2.69, 2.70)	2.70 (2.69, 2.71)	2.69 (2.68, 2.70)	0.195
Model 2	2.69 (2.69, 2.70)	2.70 (2.69, 2.70)	2.70 (2.69, 2.70)	2.69 (2.68, 2.70)	0.256
Model 3	2.69 (2.69, 2.70)	2.70 (2.69, 2.70)	2.70 (2.69, 2.70)	2.69 (2.68, 2.70)	0.261
1-back task					
Model 1	1.30 (1.29, 1.30)	1.30 (1.29, 1.31)	1.28 (1.26, 1.30)	1.24 (1.22, 1.27)*	<0.001
Model 2	1.30 (1.29, 1.30)	1.30 (1.29, 1.31)	1.28 (1.26, 1.30)	1.24 (1.22, 1.27)*	<0.001
Model 3	1.29 (1.29, 1.30)	1.30 (1.29, 1.31)	1.28 (1.26, 1.30)	1.25 (1.22, 1.27)*	<0.001
1-card-learning task					
Model 1	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.95 (0.93, 0.96)	0.93 (0.91, 0.94)	0.022
Model 2	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.95 (0.94, 0.96)	0.93 (0.92, 0.94)	0.063
Model 3	0.95 (0.94, 0.95)	0.95 (0.94, 0.96)	0.95 (0.94, 0.96)	0.93 (0.92, 0.95)	0.206

Values are adjusted means and 95% CI. *P* value: overall difference between 4 coronary artery calcium categories. Model 1: adjusted for age. Model 2: adjusted for age, sex, educational level. Model 3: Model 2 plus adjusted for current smoking, body mass index, hypertension, hypercholesterolemia, and diabetes mellitus.

*Post hoc tests, compared with coronary artery calcium 0, $P<0.05$.

Table 3. Association of Severity of Coronary Artery Calcium With Cognitive Function Per Test by Age Strata

Cognitive tasks and Models	Coronary Artery Calcium Categories				*P* Value
	0	1–99	100–399	≥400	
Aged 45–54 y, n=2027					
Detection task					
Model 1	2.53 (2.52, 2.53)	2.53 (2.51, 2.54)	2.52 (2.49, 2.55)	2.56 (2.51, 2.61)	0.595
Model 2	2.53 (2.52, 2.53)	2.52 (2.51, 2.54)	2.52 (2.48, 2.55)	2.55 (2.50, 2.60)	0.646
Model 3	2.53 (2.52, 2.53)	2.52 (2.51, 2.54)	2.52 (2.48, 2.55)	2.55 (2.50, 2.60)	0.679
Identification task					
Model 1	2.67 (2.66, 2.67)	2.67 (2.66, 2.67)	2.68 (2.66, 2.70)	2.66 (2.64, 2.68)	0.388
Model 2	2.67 (2.66, 2.67)	2.67 (2.66, 2.67)	2.68 (2.66, 2.69)	2.66 (2.64, 2.68)	0.489
Model 3	2.67 (2.66, 2.67)	2.67 (2.66, 2.67)	2.68 (2.66, 2.69)	2.66 (2.63, 2.68)	0.480
1-back task					
Model 1	1.33 (1.32, 1.34)	1.34 (1.32, 1.35)	1.29 (1.25, 1.33)	1.21 (1.15, 1.27)*	<0.001
Model 2	1.32 (1.32, 1.34)	1.34 (1.32, 1.35)	1.29 (1.25, 1.33)	1.22 (1.16, 1.28)*	<0.001
Model 3	1.32 (1.31, 1.33)	1.34 (1.32, 1.36)	1.29 (1.25, 1.34)	1.23 (1.16, 1.29)*	0.001
1-card-learning task					
Model 1	0.96 (0.96, 0.97)	0.96 (0.95, 0.97)	0.96 (0.93, 0.98)	0.93 (0.90, 0.97)	0.486
Model 2	0.96 (0.96, 0.97)	0.96 (0.95, 0.97)	0.96 (0.93, 0.99)	0.94 (0.90, 0.98)	0.707
Model 3	0.96 (0.96, 0.97)	0.97 (0.96, 0.98)	0.96 (0.94, 0.99)	0.95 (0.91, 0.98)	0.691
Aged 55–64 y, n=1960					
Detection task					
Model 1	2.59 (2.57, 2.60)	2.59 (2.57, 2.60)	2.57 (2.55, 2.60)	2.57 (2.54, 2.61)	0.651
Model 2	2.59 (2.58, 2.60)	2.59 (2.57, 2.60)	2.57 (2.55, 2.59)	2.57 (2.53, 2.61)	0.527
Model 3	2.59 (2.57, 2.60)	2.59 (2.57, 2.60)	2.57 (2.55, 2.59)	2.57 (2.53, 2.61)	0.623
Identification task					
Model 1	2.69 (2.69, 2.70)	2.70 (2.70, 2.71)	2.68 (2.67, 2.70)	2.68 (2.67, 2.70)	0.013
Model 2	2.69 (2.69, 2.70)	2.70 (2.70, 2.71)	2.68 (2.67, 2.70)	2.68 (2.67, 2.70)	0.015
Model 3	2.69 (2.69, 2.70)	2.70 (2.69, 2.71)	2.68 (2.67, 2.69)	2.68 (2.66, 2.70)†	0.010
1-back task					
Model 1	1.29 (1.29, 1.30)	1.29 (1.28, 1.31)	1.28 (1.25, 1.31)	1.24 (1.20, 1.28)	0.100
Model 2	1.29 (1.28, 1.30)	1.29 (1.28, 1.31)	1.28 (1.25, 1.31)	1.24 (1.20, 1.28)	0.107
Model 3	1.29 (1.28, 1.30)	1.29 (1.28, 1.31)	1.28 (1.25, 1.31)	1.25 (1.20, 1.29)	0.201
1-card-learning task					
Model 1	0.95 (0.95, 0.96)	0.94 (0.94, 0.95)	0.94 (0.93, 0.96)	0.93 (0.90, 0.95)	0.149
Model 2	0.95 (0.95, 0.96)	0.95 (0.94, 0.95)	0.94 (0.93, 0.96)	0.93 (0.91, 0.95)	0.305
Model 3	0.95 (0.94, 0.96)	0.95 (0.94, 0.96)	0.95 (0.93, 0.96)	0.93 (0.91, 0.96)	0.678
Aged ≥65 y, n=1001					
Detection task					
Model 1	2.68 (2.65, 2.70)	2.68 (2.66, 2.70)	2.68 (2.65, 2.71)	2.68 (2.65, 2.71)	0.990
Model 2	2.67 (2.64, 2.70)	2.68 (2.65, 2.70)	2.68 (2.65, 2.71)	2.69 (2.66, 2.72)	0.826
Model 3	2.67 (2.64, 2.70)	2.68 (2.65, 2.70)	2.68 (2.65, 2.71)	2.69 (2.66, 2.72)	0.745
Identification task					
Model 1	2.74 (2.73, 2.76)	2.74 (2.73, 2.75)	2.76 (2.75, 2.78)	2.74 (2.73, 2.75)	0.042
Model 2	2.74 (2.73, 2.76)	2.74 (2.73, 2.75)	2.76 (2.75, 2.78)	2.74 (2.73, 2.76)	0.050
Model 3	2.74 (2.73, 2.76)	2.74 (2.73, 2.75)	2.76 (2.75, 2.78)	2.74 (2.73, 2.76)	0.055
1-back task					
Model 1	1.24 (1.21, 1.27)	1.24 (1.22, 1.27)	1.23 (1.20, 1.27)	1.20 (1.17, 1.24)	0.321
Model 2	1.24 (1.21, 1.28)	1.24 (1.22, 1.27)	1.24 (1.20, 1.27)	1.20 (1.17, 1.24)	0.301

(*Continued*)

Table 3. Continued

Cognitive tasks and Models	Coronary Artery Calcium Categories				*P* Value
	0	1–99	100–399	≥400	
Model 3	1.24 (1.21, 1.28)	1.24 (1.22, 1.27)	1.24 (1.20, 1.27)	1.20 (1.17, 1.24)	0.303
1-card learning task					
Model 1	0.92 (0.90, 0.94)	0.92 (0.91, 0.93)	0.92 (0.91, 0.94)	0.91 (0.89, 0.92)	0.425
Model 2	0.92 (0.90, 0.94)	0.92 (0.91, 0.93)	0.93 (0.91, 0.94)	0.91 (0.89, 0.92)	0.475
Model 3	0.92 (0.90, 0.94)	0.92 (0.91, 0.93)	0.93 (0.91, 0.94)	0.91 (0.89, 0.93)	0.533

Values are adjusted means and 95% CI. *P* value: overall difference between 4 coronary artery calcium categories. Model 1: adjusted for age. Model 2: adjusted for age, sex, educational level. Model 3: Model 2 plus current smoking, body mass index, hypertension, hypercholesterolemia, diabetes mellitus.

*Post hoc tests, compared with coronary artery calcium 0, $P<0.05$.

†Post hoc tests, compared with coronary artery calcium 1 to 99, $P<0.05$.

an inverse trend with increasing CAC scores, independent of cardiovascular risk factors. This inverse relationship of CAC score categories with working memory was strongest in participants aged 45 to 54 years. In participants aged 45 to 54 years, the mean OBK score of CAC ≥400 was 0.09 points lower than CAC 0.

Prior studies that investigated associations between CAC and cognitive function showed mixed results. In general, higher CAC scores were associated with worse performance in processing speed, despite heterogeneities in study population and cognitive tests.[7–10] In the Rotterdam study, a prospective study among elderly (mean age 69.4±6.7 years), increased CAC was associated with accelerated decline in processing speed and higher risk of dementia.[7] In cross-sectional studies, an inverse association between CAC and cognitive function was also found. Particularly, in the CARDIA study among middle-aged adults (43–55 years), a higher CAC category was associated with a worse performance of processing speed, sustained attention, and working memory.[10] In the ELSA-Brasil study (mean age 50.9±8.8 years, range 35–74 years), higher CAC scores were associated with worse performance of processing speed, executive function, and attention. In the AGES-Reykjavik study among elderly (mean age 76.3±5.4 years), lower scores on processing speed and executive function were strongly related to higher CAC score, but the relation between CAC and memory was not significant in fully adjusted analyses.[9] In our study, we did not find a relation between CAC severity and processing speed as assessed by the detection task. Besides heterogeneities in population, a potential explanation of this lack of association may be because of the different test we used. In prior studies, processing speed was measured by the digit symbol substitution test or the trail-making test.[7–10] These tests are sensitive and validated tools and have been extensively used in neuropsychological assessment for decades.[24,25] Although significant correlations were found between DET with the trail-making test and digit symbol test, the magnitude of the correlations was low, suggesting that DET may not be 1-to-1 mapped to the trail-making test or the digit symbol test.[18]

In our study, working memory showed an inverse trend with increasing CAC scores, independent of cardiovascular risk factors. Moreover, this inverse relationship of CAC score categories with working memory was strongest in participants aged 45 to 54 years. This result was similar to the CARDIA study that was conducted in middle-aged adults (43–55 years).[10] We found that in participants aged 45 to 54 years, the OBK score in CAC ≥400 was 0.09 lower than in CAC 0 category. To put this into context, in the current study the OBK score was 0.004 lower for every 1-year increase in age. This implies that the difference in OBK scores that was observed between CAC ≥400 and CAC 0 may correspond to a difference of 20 years.

Impairment in working memory task has been observed in many neurodegenerative diseases including Alzheimer disease and vascular dementia.[26] In our study, the observed association between severe CAC and declined working memory may be explained by the concept that CAC is a marker that reflects the lifetime exposure to (un)known risk factors shared between cardiovascular disease and noncardiovascular disease including dementia.[6,27,28] This exposure to risk factors may also have resulted in damage to vulnerable brain structures that are involved in memory function, but this needs to be further investigated. Another explanation for the association is that CAC may reflect generalized atherosclerosis including that in the coronary arteries and also in cerebral vessels. Atherosclerotic lesions in cerebral vessels may result in chronic cerebral hypoperfusion, which may consequently lead to cognitive impairment.[29] On the other hand, in our study, the lack of significant association between CAC and cognitive function in participants aged ≥65 years may be because of the selective survival bias wherein participants with severe CAC who were likely to have worse cognitive performance may not have survived to participate in this study.

The main strengths of this study were as follows. First, this study comprises a large population-based sample with a wide age range, which allows age-stratified analyses of associations between CAC severity and cognitive function. Second, embedded in the Lifelines cohort, standardized protocols with quality control were used for the comprehensive data collection on potential confounders including educational level, lifestyle, and cardiovascular risk factors. Third, 4 core cognitive domains were assessed by the CogState Brief Battery. CogState Brief Battery, a collection of computerized tests with good test–retest reliability, which are less time-consuming and labor-intensive, has been developed to monitor cognitive changes in large population-based studies with wide age ranges.[18,30] This study also had limitations. An important limitation was that there was an interval of 2 to 6 years between the assessment of cognitive function and CAC scoring. It is possible that less healthy participants, especially those who had worse cognitive performance, were not able to participate in the ImaLife study and therefore did not undergo CAC scoring. This may lead to an underestimation of the magnitude of the inverse association between CAC severity and cognitive function, especially in the elderly. Second, this study was a cross-sectional analysis of associations between CAC severity and cognitive testing of different domains at a single time point. Therefore, it is not possible to assess whether increasing CAC severity is associated with accelerated cognitive decline over time or earlier onset of dementia. Third, although we excluded participants with self-reported history of stroke, given lack of brain imaging in Lifelines, we were not able to investigate whether the association between increased CAC severity and worse cognitive performance is mediated by cerebral lesions. Further research of the mechanistic pathways between atherosclerotic burden and cognitive impairment is needed.

CONCLUSIONS

In conclusion, increasing CAC score was associated with worse performance of working memory in a large population-based Dutch cohort aged ≥45 years. This association was independent of classical cardiovascular risk factors. The inverse relationship of CAC score categories with working memory was strongest in participants aged 45 to 54 years. These findings suggest that CAC scoring may potentially identify individuals at risk of cognitive dysfunction, although longitudinal studies are needed to confirm that CAC is an independent predictor of cognitive impairment and dementia.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Association of severity of coronary artery calcium with cognitive function per test.

	Coronary artery calcium categories								
	0		1-99		100-399		≥400		P
Detection task									
Model 4	2.58	(2.57, 2.59)	2.58	(2.57, 2.59)	2.57	(2.56, 2.59)	2.58	(2.56, 2.60)	0.728
Identification task									
Model 4	2.69	(2.69, 2.70)	2.70	(2.69, 2.70)	2.70	(2.69, 2.70)	2.69	(2.68, 2.70)	0.225
One back task									
Model 4	1.29	(1.29, 1.30)	1.30	(1.29, 1.31)	1.28	(1.26, 1.30)	1.25	(1.22, 1.27)*	***<0.001***
One card learning task									
Model 4	0.95	(0.94, 0.95)	0.95	(0.94, 0.96)	0.95	(0.94, 0.96)	0.93	(0.92, 0.95)	0.185

Values are adjusted means and 95% confidence interval.

P value: overall difference between four coronary artery calcium categories

* *Post hoc* tests, compared to CAC zero p< 0.05

Model 4: adjusted for age, sex, educational level, current smoking, body mass index, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low-density lipoprotein cholesterol

Table S2. Association of severity of coronary artery calcium with cognitive function per test by age strata.

	Coronary artery calcium categories								
	0		1-99		100-399		≥400		P
Aged 45-54 years, n=2,027									
Detection task									
Model 4	2.53	(2.52, 2.54)	2.52	(2.51, 2.54)	2.51	(2.48, 2.55)	2.56	(2.51, 2.61)	0.528
Identification task									
Model 4	2.67	(2.66, 2.67)	2.67	(2.66, 2.67)	2.68	(2.66, 2.69)	2.66	(2.64, 2.68)	0.658
One back task									
Model 4	1.32	(1.31, 1.33)	1.34	(1.32, 1.36)	1.29	(1.25, 1.34)	1.22	(1.16, 1.28)*	***0.001***
One card learning task									
Model 4	0.96	(0.96, 0.97)	0.97	(0.96, 0.98)	0.96	(0.93, 0.99)	0.94	(0.90, 0.98)	0.621
Aged 55-64 years, n=1,960									
Detection task									
Model 4	2.59	(2.58, 2.60)	2.59	(2.57, 2.60)	2.57	(2.55, 2.60)	2.57	(2.54, 2.61)	0.613
Identification task									
Model 4	2.69	(2.69, 2.70)	2.70	(2.70, 2.71)	2.68	(2.67, 2.69)	2.68	(2.66, 2.70)#	***0.006***
One back task									
Model 4	1.29	(1.28, 1.30)	1.29	(1.28, 1.31)	1.28	(1.25, 1.30)	1.25	(1.20, 1.29)	0.182
One card learning task									
Model 4	0.95	(0.94, 0.96)	0.95	(0.94, 0.96)	0.95	(0.93, 0.96)	0.94	(0.91, 0.96)	0.714
Aged ≥65 years, n=1,001									
Detection task									
Model 4	2.67	(2.64, 2.70)	2.68	(2.65, 2.70)	2.68	(2.65, 2.71)	2.69	(2.66, 2.72)	0.780
Identification task									
Model 4	2.74	(2.73, 2.76)	2.74	(2.73, 2.75)	2.76	(2.75, 2.78)	2.74	(2.73, 2.75)	0.088
One back task									
Model 4	1.24	(1.21, 1.27)	1.24	(1.22, 1.27)	1.24	(1.20, 1.27)	1.21	(1.17, 1.24)	0.416
One card learning task									
Model 4	0.92	(0.90, 0.93)	0.92	(0.91, 0.93)	0.92	(0.91, 0.94)	0.91	(0.89, 0.93)	0.649

Values are adjusted means and 95% confidence interval.

P value: overall difference between four coronary artery calcium categories

* *Post hoc* tests, compared to CAC zero p< 0.05

Post hoc tests, compared to CAC 1-99 p< 0.05

Model 4: adjusted for age, sex, educational level, current smoking, body mass index, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low-density lipoprotein cholesterol