Association of arterial stiffness with coronary artery calcium score in the general-population: the Swedish CArdioPulmonary bioImage study

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INTRODUCTION

With increasing age, the walls of large elastic arteries undergo adverse structural and functional changes, leading to arterial stiffness or arteriosclerosis. This is mainly influenced by changes in the tunica media layer including increase in amount of collagen and decrease in elastin \cite{[1]}. Arterial stiffness can be determined by various indices, but carotid femoral pulse wave velocity (c-f PWV) is the most widely validated, and is considered the gold standard \cite{[2]}. In addition to age, hypertension is an important determinant of elevated PWV \cite{[3]}. Arterial stiffness is a well documented predictor of all-cause mortality and future cardiovascular events \cite{[4]}. Although the process of arterial stiffening often is paralleled by arteriosclerosis, there are important differences between the two. While arteriosclerosis is focused on morphological changes in the tunica media, arterosclerosis is characterized by deposition of lipids, foam cells and calcium in the tunica intima \cite{[5]}, as well as frequent distribution into the fat surrounding the arterial wall. Importantly, arteriosclerosis is associated with a loss of volume-buffering, cushioning function, known as the Windkessel effect, in large arteries whereas arterosclerosis is characterized by a disturbed conduit function \cite{[6]}.

Despite considerable advances in medicine, prevention of arteriosclerotic disease in asymptomatic patients remains challenging. An important measure of sub-clinical arteriosclerosis is coronary artery calcium score (CACS). Recent studies have suggested that increased arterial stiffness is associated with a higher odds of having a CACS category >100 (OR: 1.25, 95% CI 1.14–1.36) in the final multivariable model. One standard deviation increase in c-f PWV was independently associated with a higher odds of having CACS category >100 (OR: 1.25, 95% CI 1.14–1.36) in the final multivariable model.

**Conclusion:** c-f PWV is positively associated with increased risk of higher CACS, and can be valuable in identifying individuals at risk for sub-clinical arteriosclerosis.

**Objectives:** Coronary artery calcium score (CACS) is a marker of subclinical atherosclerosis. However, there is little data related to the association between arterial stiffness and CACS in the general population. The aim of this study was to explore the association between carotid femoral-pulse wave velocity (c-f PWV), a widely accepted marker of arterial stiffness, and CACS.

**Methods:** Participants with complete measurements on c-f PWV, CACS and confounding variables from the Swedish CArdioPulmonary bioImage Study (SCAPIS) cohort were included in the final study population (n = 8725). CACS was divided into three categories (<10, >10 and ≤100, and >100) and multinomial logistic regression was performed to explore the association between these categories of CACS and quartiles of c-f PWV, and for per one standard deviation (SD) increment of c-f PWV.

**Results:** CACS ≤10, >10 and ≤100, and >100 were present in 69.3, 17.8 and 12.9% of the study population, respectively. The odds ratio (OR) for CACS >100 for the fourth quartile (Q4) of c-f PWV vs. Q1 (reference category) was 1.62 (95% confidence interval [CI] 1.25–2.12) after adjustments. One standard deviation increase in c-f PWV was independently associated with a higher odds of having a CACS category >100 (OR: 1.25, 95% CI 1.14–1.36) in the final multivariable model.

**Conclusion:** c-f PWV is positively associated with increased risk of higher CACS, and can be valuable in identifying individuals at risk for sub-clinical atherosclerosis.

**Keywords:** arterial stiffness, arteriosclerosis, cohort, coronary artery calcium score, epidemiology

**Abbreviations:** b-a PWV, brachial-ankle pulse wave velocity; CACS, coronary artery calcium score; C-f PWV, carotid-femoral pulse wave velocity; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; HR, hazard ratio; LLQ, lower limit of quantification; MAP, mean arterial pressure; OR, odds ratio; SCAPIS, Swedish CArdioPulmonary bioImage Study
studies have suggested that CACS is of predictive value, particularly in asymptomatic subjects [7–11]. Evidence from the Multi-Ethnic Study of Atherosclerosis (MESA) indicates that CAC scoring can significantly help to reclassify those at risk [12]. Both arterial stiffness and CACS are important predictors for adverse cardiovascular outcomes in the general population. What is not well known, however, is the effect of arterial stiffness on the risk of higher CACS. Few studies have explored the association between these two parameters. However, these studies have either used brachial-ankle PWV (b-a PWV) as a determinant for stiffness or included relatively smaller sample sizes. b-a PWV is another parameter used to measure arterial stiffness. However, it reflects arterial stiffness over a longer arterial length and includes both elastic and muscular arteries, and has shown weaker evidence for cardiovascular disease prediction [13].

Therefore, the aim of our observational study was to investigate the cross-sectional association between arterial stiffness, as determined by c-f PWV, and CACS in a large middle-aged population cohort.

MATERIALS AND METHODS

Study population

The Swedish CArdioPulmonary bio Image Study (SCAPIS) is a collaborative multicenter project conducted at six Swedish university hospitals (Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå and Uppsala) [14]. The project was initiated to study risk factors for cardiovascular and pulmonary diseases using advanced imaging of pulmonary and cardiovascular structure and function. 30,154 participants aged 50–64 years, including both men and women, were enrolled by random selection from the Swedish population register. The overall participation rate for SCAPIS was 49.5%. The study included completion of a comprehensive questionnaire, biochemistry analysis, anthropometric measurements and extensive imaging. Some measurements were unique to a center and were not carried out at other sites. The c-f PWV measurements were conducted in Malmö (6251 individuals, 53% participation rate) and Linköping (5057 individuals, 58% participation rate). All those who had at least two measurements of c-f PWV were included in the study population. Moreover, those with missing value for CACS and missing value of other co-variates were excluded. The final study population was 8725 (Malmö = 5558, Linköping = 3167). The flow chart for the study population is presented in Figure 1. The study was approved by the Regional Ethical Review Board in Umeå (2010-228-31 M), Lund (2016/1031) and Linköping (2018/478-31). Written informed consent was obtained from the participants.

Carotid femoral pulse wave velocity assessment

Arterial stiffness was determined by the parameter c-f PWV, using device Sphygmocor Xcel (Atcor Medical, Australia) [15]. Participants were advised to refrain from caffeine, heavy meal for 3 h, nicotine for 4 h and alcohol for 12 h prior to the examination. Blood pressure cuffs were attached to the upper left arm and to the right thigh approximately 10–20 cm below the groin. The distances were measured from the carotid pulse to the upper edge of the thigh cuff, and from the femoral pulse to upper edge of the thigh cuff. Both these distances were multiplied by 0.8. The final distance was calculated by subtracting the distance between the femoral pulse and the upper margin of the thigh cuff (multiplied by 0.8) from the distance between the carotid receptor and the thigh cuff (multiplied by 0.8) [16]. This final distance was divided by the time difference between the signal registered from the tonometer at the carotid artery and simultaneous capturing of the signal from the femoral cuff, to obtain c-f PWV measurement.

At each assessment, c-f PWV was measured twice. If the difference between the measurements was >0.5 m/s, a third measurement was done. The participants with two values

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**FIGURE 1** Flow chart of the study population.
for c-f PWV were included in the study and the average mean of the measurements was used in the analysis. Mean arterial pressure (MAP) was calculated as \((2 \times \text{diastolic pressure} + \text{systolic pressure})/3\), where the systolic and diastolic pressures were measured before the c-f PWV measurement.

**Coronary artery calcium score measurement**

Computed tomography (CT) was used to determine CACS, and measurements were done on an average 7.6 days after c-f PWV measurements. Non contrast CT was performed using a dedicated dual-source CT scanner equipped with a Stellar Detector (Somatom Definition Flash; Siemens Medical Solution, Forchheim, Germany) [14]. Participants were excluded from CACS measurement in case of presence of cardiac stent or history of by-pass surgery. Calcium content in each artery was measured and summed utilizing the scoring system elaborated by Agatston et al. [17–19].

**Covariates measurement**

Waist circumference (cm) was measured midway between the lowest rib margin and the iliac crest. Venous blood was drawn after over-night fasting and was immediately analyzed for high-density lipoprotein cholesterol (HDL-C) and high sensitive C-reactive protein (hs-CRP). Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald’s formula at the Linkoping site and was determined by direct measurement using Cobas 501 at the Malmö site. Brachial systolic blood pressure readings were taken before the c-f PWV measurement using the Sphygmocor Xcel device using the same cuff as for PWV measurement in the left arm after 5 min of rest in supine position in Malmö. In Linkoping, a Dinamap monitor was used for blood pressure measurement. Information regarding smoking status, use of antihypertensive and antilipid medication was obtained from the questionnaire. Prevalent diabetes was determined by report of a prior diagnosis of diabetes in the questionnaire or new cases identified at baseline.

**Statistical analysis**

hs-CRP was log transformed due to its skewed distribution. hs-CRP levels below lower limit of quantification (LLQ, 0.6 mg/L) were replaced with a value of LLQ/\(\sqrt{2}\). More than 50% of the population had a calcium score of zero giving a positively skewed data. For the purpose of our analysis, CACS was classified into three categories using cut offs: \(\leq 10\), \(> 10\) and \(\leq 100\), and \(>100\) to indicate low, intermediate and high risk [20]. CACS was also explored as a continuous variable. A constant (+1) was added to CACS before log transformation due to many zero values. Analysis based on the Bland—Altman plot was conducted to test for agreement between the two measurements of c-f PWV along with use of linear regression to evaluate the relationship. The participants were categorized into quartiles according to increasing c-f PWV. Such quartiles were also created separately for men and women for additional analysis stratified for sex. The characteristics of the study population were explored and described as mean ± standard deviation (SD) for normal distributions, median (25th–75th percentiles) for skewed distributions, or as proportions for categorical variables for the whole cohort and across the quartiles of c-f PWV. We tested differences across the various characteristics using \(\chi^2\) for categorical variables and ANOVA for continuous variables.

Multinomial logistic regression was used to assess the association between quartiles of c-f PWV and three categories of CACS for the study population, and then for the sex-stratified analysis. In addition, we calculated the odds ratio (OR) of CACS for per 1 SD increment of c-f PWV, again for the overall cohort and stratified for sex. Additionally, multivariable linear regression analysis was conducted to assess the relationship between c-f PWV and CACS as a continuous variable \(\ln(\text{CACS} + 1)\). Three different models were created for all these analyses. Model 1 was adjusted for age, sex, MAP and average heart rate. Model 2 was further adjusted for waist, diabetes, LDL, HDL, smoking status, brachial systolic blood pressure and hs-CRP. Model 3 was additionally adjusted for use of antihypertensive drugs and antilipid medication. All models were also adjusted for site. The covariates were considered potential confounders based on literature review of known risk factors as presented in a directed acyclic graph, DAG (Figure 1, Supplemental Digital Content, http://links.lww.com/HJH/B862).

Interactions between c-f PWV and risk factors such as age, sex, smoking and hs-CRP were investigated by introducing interaction terms in the final multivariable model. The added predictive value of c-f PWV to the models was evaluated using C-statistics (corresponding to area under the receiver operating curve, ROC) and the likelihood ratio (LR) test. These were assessed for two separate binary outcomes in separate logistic regression models, that is CACS \(\leq 10\) and \(> 10\) and CACS \(\leq 100\) and \(> 100\). All analysis was carried out using SPSS version 26 (IBM Corp., Armonk, New York, USA) and STATA version 12 (StataCorp, College Station, Texas, USA). A P value of \(<0.05\) was regarded as statistically significant.

**RESULTS**

The baseline characteristics of the study population across the four quartiles of c-f PWV are presented in Table 1. The mean value of c-f PWV was 8.53 m/s for the whole study population. Those in the highest quartile of c-f PWV had significantly higher mean age, MAP and systolic blood pressure, waist and heart rate, as compared to those in the lower quartiles. Moreover, there were higher proportions of patients with diabetes and those using antihypertensive and/or antilipid medication in the highest quartile. Approximately 69.3%, 17.8% and 12.9% of the whole study population had CACS of \(\leq 10\), \(> 10\) and \(\leq 100\), and \(>100\), respectively. Individuals who were excluded from the final study population had similar baseline characteristics (mean age: 57.61 ± 4.38 years, men: 51.2%). There were slightly less smokers (11.7%) but had higher mean blood pressure \((n = 1045, 132 ± 16.7 \text{ mmHg})\). The Bland–Altman plot used for testing reproducibility of the two c-f PWV measurements displayed no proportional bias (Figure 2, Supplemental Digital Content, http://links.lww.com/HJH/B862), and testing with linear regression showed good agreement between the two measurements.
The LR test showed that after adding c-f PWV to binary logistic regression (CACS > 10) with Model 3 covariates, this resulted in a significantly likelier model (P < 0.001). The C-statistics improved marginally from 0.746 to 0.748 (P value for difference = 0.006) (Figure 3, Supplemental Digital Content, http://links.lww.com/HJH/B862). Similarly, the LR test showed a likelier model after addition of c-f PWV for the binary logistic regression (CACS > 10) to other covariates in Model 3. There was a small but nonsignificant improvement in C-statistics from 0.770 to 0.772 (P value for difference = 0.057) (Figure 4, Supplemental Digital Content, http://links.lww.com/HJH/B862).

DISCUSSION

The results of our cross-sectional study show that there is an association between arterial stiffness and increased risk of CACS. The association remained statistically significant even after adjusting for other potential cardiovascular risk factors. We did not observe any significant effect modification of the association between c-f PWV and CACS in relation to sex, suggesting that risk of higher CACS is similar in men and women. Although the results are not significant in women for the higher CACS, this might be due to lower number of participants in the higher CACS category when stratified for sex.

To our knowledge this is the largest epidemiological study to date exploring the relationship between arterial stiffness (atherosclerosis), using c-f PWV, and atherosclerosis, using CACS. The results of our study are in line with several previous studies [21–26] that explored the association between various other indices of arterial stiffness and CACS, or were conducted on a relatively smaller scale. The

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### TABLE 1. Baseline characteristics

| Characteristics | Whole population | Q1 | Q2 | Q3 | Q4 | P value* |
|-----------------|------------------|----|----|----|----|--------|
| Number of participants (n) | 8725 | 2170 | 2207 | 2177 | 2171 |         |
| Average c-f PWV (m/s) | 8.53 (±1.31) | 7.05 (±0.46) | 8.00 (±0.21) | 8.79 (±0.25) | 10.27 (±0.97) |         |
| Mean arterial pressure (mmHg) | 93.67 (86.67–101) | 85.47 (±8.31) | 91.76 (±8.22) | 96.51 (±8.85) | 103.49 (±9.94) | < 0.001 |
| Systolic blood pressure (mmHg) | 128.10 (±15.46) | 116.17 (±11.42) | 124.62 (±11.64) | 130.70 (±12.76) | 140.94 (±14.25) | < 0.001 |
| Average heart rate (beats/min) | 61.07 (±9.05) | 58.54 (±8.03) | 60.13 (±8.45) | 61.76 (±9.20) | 63.88 (±9.56) | < 0.001 |
| Age (years) | 57.41 (±7.18) | 55.94 (±4.11) | 56.99 (±4.22) | 57.71 (±4.27) | 59.03 (±4.13) | < 0.001 |
| LDL-C (mmol/l) | 3.51 (±0.96) | 3.49 (±0.93) | 3.50 (±0.95) | 3.52 (±0.96) | 3.52 (±0.99) | 0.730 |
| HDL-C (mmol/l) | 1.67 (±0.52) | 1.80 (±0.52) | 1.70 (±0.52) | 1.63 (±0.50) | 1.55 (±0.50) | < 0.001 |
| Waist (cm) | 93.74 (±12.65) | 89.21 (±11.96) | 92.64 (±12.21) | 95.13 (±12.43) | 97.97 (±12.32) | < 0.001 |
| CRP (mg/l)* | 1.0 (0.60–2.42) | 0.90 (0.60–1.90) | 1.00 (0.60–2.42) | 1.10 (0.60–2.42) | 1.42 (0.60–2.42) | < 0.001 |
| Men (n, %) | 4138 (47.4) | 646 (29.8) | 946 (42.9) | 1122 (51.5) | 1424 (65.6) | < 0.001 |
| Diabetes (n, %) | 623 (7.1) | 69 (3.2) | 122 (5.5) | 162 (7.4) | 175 (8.0) | < 0.001 |
| Nonsmokers | 4262 (48.8) | 1051 (48.4) | 1109 (50.2) | 1050 (48.2) | 1052 (48.5) | 0.242 |
| Ex-smokers | 3188 (36.5) | 778 (35.9) | 775 (35.1) | 809 (37.2) | 826 (38.0) | < 0.001 |
| Current smokers | 622 (7.1) | 88 (4.1) | 140 (6.3) | 175 (8.0) | 219 (10.1) | < 0.001 |
| Coronary artery calcium score (CAC score) (n, %) | 1275 (14.6) | 341 (15.7) | 323 (14.6) | 318 (14.6) | 293 (13.5) | < 0.001 |

Values expressed are means (±SD) or percentages unless specified otherwise.

*Median (25–75%).

* P value is for difference across the quartiles of c-f PWV.

c-f PWV, carotid femoral-pulse wave velocity; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.
study of Kullo et al. [21] explored the association between aortic PWV in a community-based sample of around 400 participants, and demonstrated that CACS was positively associated with PWV. Similar results were observed in a study of around 800 participants in a cohort enriched for hypertension [22]. Another example of a study exploring the association between c-f PWV and CACS is the Rotterdam study, where the association in an elderly population (mean age 71 years) was explored, and showed strong association of c-f PWV with coronary atherosclerosis [23]. Ageing is a significant risk factor for both increasing arterial stiffness and calcium deposition. The results of our study show that this association is present in a relatively younger (middle-aged) cohort.

Other parameters of arterial stiffness have also been explored in relation to CACS. A cross-sectional study conducted in men in Japan showed that elevated b-a PWV, a measure of peripheral and central arterial stiffness, was associated with increased prevalence of CACS after accounting for potential confounders [24]. Another study conducted in a Korean cohort linked b-a PWV with progression of CACS over a period of 2.7 median years [25]. A large-scale study of asymptomatic participants using b-a PWV as a measure of arterial stiffness reported similar association between elevated b-a PWV and severity of CACS [26]. In another cross-sectional study, Vishnu et al. [27] explored the association between ba-PWV and CACS in a general population of around 1130 healthy men. Their results showed that ba-PWV was significantly associated with presence of CAC in different races. A similar association of ba-PWV with CACS was reported among obese postmenopausal women in the US [28]. Conversely, an early study reported conflicting results. Megnien et al. [29] conducted a study in asymptomatic men at cardiovascular risk and did not find any association between c-f PWV and coronary artery calcium deposit.

In summary, all these studies taken together show that arterial stiffness is associated with atherosclerosis using CACS as the index. Our study adds to the existing knowledge of association between PWV and CACS by evaluating association in a large population-based sample. Many plausible mechanisms can be considered for this observed

### Table 2: Association between c-f PWV quartiles, c-f PWV per SD and CACS categories

|          | Q1              | Q2              | Q3              | Q4              | OR per SD |
|----------|-----------------|-----------------|-----------------|-----------------|-----------|
| Whole cohort | n = 2170 (3.85–7.60) | n = 2207 (7.64–8.36) | n = 2177 (8.40–9.25) | n = 2171 (9.28–18.30) |           |
| Model 1 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.22 (1.01–1.46)*   | 1.44 (1.19–1.73)**  | 1.66 (1.34–2.05)**  | 1.18 (1.10–1.28)** |
| CACS > 100 |               | 1.14 (0.91–1.44)   | 1.35 (1.07–1.71)*   | 1.78 (1.38–2.30)**  | 1.30 (1.20–1.42)** |
| Model 2 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.21 (1.00–1.45)*   | 1.40 (1.16–1.70)**  | 1.58 (1.27–1.96)**  | 1.15 (1.07–1.25)** |
| CACS > 100 |               | 1.12 (0.89–1.42)   | 1.31 (1.03–1.66)*   | 1.64 (1.26–2.13)**  | 1.25 (1.14–1.36)** |
| Model 3 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.20 (1.00–1.45)*   | 1.40 (1.15–1.69)**  | 1.57 (1.27–1.96)**  | 1.15 (1.06–1.25)** |
| CACS > 100 |               | 1.15 (1.06–1.25)*** | 1.28 (1.01–1.63)*   | 1.63 (1.25–2.12)**  | 1.25 (1.14–1.36)** |

| Men | n = 1023 (5.35–7.96) | n = 1036 (8.00–8.70) | n = 1035 (8.72–9.64) | n = 1044 (9.65–17.35) |           |
|-----|----------------------|----------------------|----------------------|----------------------|-----------|
| Model 1 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.13 (0.90–1.42)   | 1.22 (0.96–1.55)     | 1.38 (1.05–1.81)*   | 1.13 (1.02–1.25)* |
| CACS > 100 |               | 1.38 (1.06–1.79)   | 1.37 (1.04–1.80)*   | 2.08 (1.55–2.80)**  | 1.31 (1.18–1.45)** |
| Model 2 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.09 (0.87–1.37)   | 1.17 (0.92–1.50)     | 1.28 (0.97–1.69)     | 1.10 (1.00–1.22)   |
| CACS > 100 |               | 1.32 (1.01–1.72)*  | 1.29 (0.98–1.71)     | 1.87 (1.38–2.53)**  | 1.26 (1.13–1.41)** |
| Model 3 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.09 (0.86–1.37)   | 1.15 (0.90–1.47)     | 1.26 (0.95–1.66)     | 1.09 (0.99–1.21)   |
| CACS > 100 |               | 1.30 (0.99–1.69)   | 1.26 (0.95–1.67)     | 1.82 (1.34–2.48)**  | 1.25 (1.12–1.39)** |

| Women | n = 1118 (3.85–7.36) | n = 1184 (7.40–8.05) | n = 1147 (8.08–8.85) | n = 1138 (8.88–18.30) |           |
|-------|----------------------|----------------------|----------------------|----------------------|-----------|
| Model 1 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.11 (0.84–1.48)   | 1.43 (1.07–1.91)*   | 1.81 (1.32–2.48)**  | 1.25 (1.12–1.39)** |
| CACS > 100 |               | 1.08 (0.73–1.60)   | 1.02 (0.68–1.53)     | 1.40 (0.91–2.16)     | 1.26 (1.10–1.44)** |
| Model 2 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.13 (0.85–1.50)   | 1.41 (1.05–1.88)*   | 1.75 (1.27–2.42)**  | 1.22 (1.08–1.36)** |
| CACS > 100 |               | 1.08 (0.72–1.61)   | 0.97 (0.64–1.47)     | 1.29 (0.83–2.00)     | 1.19 (1.04–1.37)** |
| Model 3 |                |                 |                 |                 |           |
| CACS > 10 ≤ 100 | 1               | 1.12 (0.84–1.49)   | 1.40 (1.04–1.87)*   | 1.76 (1.28–2.43)**  | 1.23 (1.10–1.37)** |
| CACS > 100 |               | 1.02 (0.68–1.53)   | 0.94 (0.62–1.43)     | 1.27 (0.81–1.97)     | 1.21 (1.05–1.39)** |

Analysis done using multinomial logistic regression. Reference category is CACS <10.
Model 1: age, sex, mean arterial pressure and average heart rate, site.
Model 2: age, sex, Mean arterial pressure, average heart rate, site, waist, DM, LDL-C, HDL-C, smoking status, brachial systolic blood pressure and CRP.
Model 3: Model 2 + antihypertensive drugs and antilipid medication.
CACS, coronary artery calcium score; c-f PWV, carotid femoral-pulse wave velocity; OR, odds ratio; SD, standard deviation.
P < 0.05.
"P < 0.01.
"P < 0.001.
n = number of participants.
Range of c-f PWV (m/s).
association. Both arterial stiffness and CACS share common cardiovascular risk factors such as age and high blood pressure [30–33] suggesting that they develop concomitantly. Another possible biological mechanism that could be suggested is that the sheer pressure on stiff arteries can lead to damage, remodeling and calcification of vessels [34]. It should be kept in mind that while CACS reflects sub-clinical atherosclerosis, c-f PWV is predominantly representative of the arteriosclerosis process. Indeed, there is overlap of risk factors between these two conditions but these are distinct processes with diverse pathological progression. These processes are not interchangeable and the measures determining them present different aspects of vascular health and ageing. However, the results of this study suggest that c-f PWV can be used as a marker for early subclinical atherosclerosis.

The C-statistics improved marginally after adding c-f PWV to the model for CACS >10 suggesting that it may add information in relation to CACS. To understand the implications of these findings, we need to evaluate the importance of CACS in the clinical context. CACS is a surrogate for subclinical CVD and aids risk stratification among asymptomatic individuals. c-f PWV measurement is a relatively simple and non-invasive procedure and has shown to be an independent predictor of cardiovascular events [4,35]. The results of our study show that c-f PWV has also high predictive value for the atherosclerotic burden and, therefore, can be helpful for optimizing the management of at-risk individuals to reduce the risk of CVD in this population. Interestingly, a recent study from the Malmo Diet and Cancer study showed that integrating carotid artery intima-media thickness and c-f PWV, reflecting arterial stiffness and atherosclerosis, into a vascular aging index improved CVD prediction [36].

A major strength of our study is the large sample size, with CACS and c-f PWV measurements conducted in standardized manner following prespecified protocols. Arterial stiffness was determined using c-f PWV, regarded as the gold standard, which has been lacking in previous studies. Some limitations need to be considered. The study has a cross-sectional design which, therefore, does not allow the temporal relationship to be assessed. Nevertheless, results show a strong magnitude of association between CACS and c-f PWV in a large general population. The participants of the study were mainly of European origin, which limits the generalizability of the results. However, prior studies summarized above conducted in other populations have shown the same direction of association. We did not have information on the calcium content in the aorta which has shown to increase arterial stiffness [37]. However, still is much unknown regarding the relationship between PWV and aortic calcification in the general population. It would be of interest to consider concurrent assessment of aortic calcification along with CACS in future imaging studies, as this may provide a more accurate assessment of sub-clinical atherosclerotic process. Nevertheless, our results show that arterial stiffness could indicate an increased risk of coronary atherosclerosis in the general population. As it is an observational study, residual confounding cannot be completely ruled out. However, information regarding other important established cardiovascular risk factors was available and taken into account while conducting the analysis.

In conclusion, the results of our study show that increased arterial stiffness, as determined by c-f PWV, is associated with sub-clinical burden of atherosclerosis as measured by CACS. The results can be of important clinical value by improving risk stratification in middle-aged populations.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. O’Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. Hypertension 2005; 45:652–658.

2. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27:2588–2605.

3. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 2009; 54:1328–1336.

4. Vlachopoulos C, Aznaroudis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55:1318–1327.

5. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med 2014; 5:927–946.

6. O’Rourke M. Mechanical principles in arterial disease. Hypertension 1995; 26:2–9.

7. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007; 49:1860–1870.
Arterial stiffness & coronary artery calcium score

8. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004; 291:210–215.
9. Greenland P, Blaha MJ, Budoff MJ, Eberl R, Watson KE. Coronary artery calcium score and cardiovascular risk. *J Am Coll Cardiol* 2018; 72:434–447.
10. Detrano R, Guerci AD, Carr JJ, Bield DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; 358:1336–1345.
11. Valenti V, B OH, Hoo R, Cho I, Schulman-Marcus J, Gransar H, et al. A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 93,715 individuals. *JACC Cardiovasc Imaging* 2015; 8:900–909.
12. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA* 2010; 303:1610–1616.
13. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Čífková R, Cosentino F, et al. The role of vascular biomarkers for primary and secondary prevention: A position paper from the European Society of Cardiology Working Group on peripheral circulation: endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015; 241:507–532.
14. Bergstrom G, Berglund G, Blomberg A, Brandberg J, Engstrom G, Engvall J, et al. The Swedish Cardiopulmonary BioImage Study: objectives and design. *Intern Med* 2015; 278:645–659.
15. Stabouli S, Printza N, Zervas C, Brodmann M, Čífková R, Cosentino F, et al. Comparison of the SphygmoCor XCEL device with applanation tonometry for pulse wave velocity and central blood pressure assessment in youth. *J Hypertens* 2019; 37:50–56.
16. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of arterial stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; 30:445–448.
17. Agatston AS, Janowitz WR, Kaplan G, Hildner F, Viamonte M Jr. Ultrafast computed tomography-detected coronary calcium reflects the angiographic extent of coronary artery atherosclerosis. *Am J Cardiol* 1994; 74:1272–1274.
18. McCollough CH, Ulzheimer S, Halliburton SS, Shanmilk K, White RD, Kalender WA. Coronary artery calcium: a multitudinal, multimanufacturer international standard for quantification at cardiac CT. *Radiology* 2007; 243:527–538.
19. Mao SS, Pal RS, McKay CR, Gao YG, Gopal A, Ahmadi N, et al. Comparison of coronary artery calcium scores between electron beam computed tomography and 64-multidetector computed tomographic scanner. *Comput Assist Tomogr* 2009; 33:175–178.
20. Kaczmarzewska E, Kępka C, Dzielnińska Z, Piacentini R, Kryczka K, Petryka J, et al. What is the optimal cut-off point for low coronary artery calcium score assessed by computed tomography? Multi-Detector Computed Tomography ANR Registry. *Postepy Kardiol Interwencyjny* 2013; 9:9–15.
21. Kullo IJ, Bielak LF, Turner ST, Sheedy PF 2nd, Pusey PA. Aortic pulse wave velocity is associated with the presence and quantity of coronary artery calcium: a community-based study. *Circulation* 2007; 115:2722–2730.
22. Laye AN, Raaz U. Killing me softly: causes and mechanisms of arterial stiffness. *JACC Cardiovasc Imaging* 2011; 3678–761.
23. van Poppele NM, Mattaccio-Raso FU, Vliegenthart R, Grobbbee DE, Asmar R, van der Kuip DA, et al. Aortic stiffness is associated with atherosclerosis of the coronary arteries in older adults: the Rotterdam study. *J Hypertens* 2006; 24:2571–2576.
24. Tori S, Arima H, Ohkubo T, Fujiyoshi A, Kadota A, Takashima N, et al. Association between pulse wave velocity and coronary artery calcification in Japanese men. *J Atheroscler Thromb* 2015; 22:1266–1277.
25. Lee JY, Ryu S, Lee SH, Kim BJ, Kim BS, Kang JH, et al. Association between brachial-ankle pulse wave velocity and progression of coronary artery calcium: a prospective cohort study. *Cardiovasc Diabetol* 2015; 14:147.
26. Gazmouz-Achirica M, Rampal S, Chang Y, Ryu S, Zhang Y, Zhao D, et al. Brachial-ankle pulse wave velocity is associated with coronary calcium in young and middle-aged asymptomatic adults: the Kangbuk Samsung Health Study. *Atherosclerosis* 2015; 241:350–356.
27. Vishnu A, Choo J, Wilcox B, Hisamatsu T, Barinas-Mitchell EJ, Fujiyoshi A, et al. Brachial-ankle pulse wave velocity is associated with coronary calcification among 1131 healthy middle-aged men. *Int J Cardiol* 2015; 189:67–72.
28. Venktachalam L, Mackey RH, Sutton-Tyrell K, Patel AS, Boraz MA, Simkin-Silverman LR, et al. Elevated pulse wave velocity increases the odds of coronary calcification in overweight postmenopausal women. *Am J Hypertens* 2007; 20:465–475.
29. Megnien JL, Simon A, Denarie N, Del-Pino M, Ganiep J, Segond P, et al. Aortic stiffening does not predict coronary and extracoronary atherosclerosis in asymptomatic men at risk for cardiovascular disease. *Am J Hypertens* 1998; 11:293–301.
30. Agatston AS, Janowitz WR, Kaplan G, Hildner F, Viamonte M Jr. Ultrafast computed tomography-detected coronary calcium reflects the angiographic extent of coronary artery atherosclerosis. *Am J Cardiol* 1994; 74:1272–1274.
31. O’Rourke MF, Safar ME, Dzau V. The cardiovascular continuum extended: aging effects on the aorta and microvasculature. *Vasc Med* 2010; 15:461–468.
32. Tay SY, Chung PV, Lao WT, Lin YC, Chung YH, Chan WP. The proper use of coronary calcium score and coronary computed tomography angiography for screening asymptomatic patients with cardiovascular risk factors. *Sci Rep* 2017; 7:17053.
33. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2007; 115:2722–2730.
34. Lyle AN, Raaz U. Killing me softly: causes and mechanisms of arterial stiffness. *JACC Cardiovasc Imaging* 2011; 37:e1–e11.
35. Ben-Shlomo Y, Speirs M, Bousted C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014; 63:656–646.
36. Nilsson Wadstrom B, Fatehali AH, Engstroım G, Nilsson PM. A vascular aging index as independent predictor of cardiovascular events and total mortality in an elderly urban population. *Angiology* 2019; 70:292–317.
37. Pedrosa JF, Brant LCC, de Aquino SA, Ribeiro AL, Barreto SM. Segmental evaluation of thoracic aortic calcium and their relations with cardiovascular risk factors in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Cells* 2021; 10:1243.