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ORIGINAL RESEARCH

Aortic Calcification is Associated with Five-Year Decline in Handgrip Strength in Older Women

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Abstract

The objective of the study was to determine the association between AAC and neuromuscular function over 5 years. Participants in this study were ambulant women over 70 years old residing in Perth, Western Australia who participated in the Calcium Intake Fracture Outcomes Study, a randomised controlled trial of calcium supplementation. 1046 women (mean age = 74.9 ± 2.6 years; BMI = 27.1 ± 4.4 kg/m^2) were included. Lateral spine images captured during bone density testing were scored for AAC (AAC24; 0–24) at baseline. Severe AAC (AAC_{sev}) was defined using established cut points (AAC24 ≥ 6). At baseline and follow-up, isometric grip strength was assessed using a dynamometer. Mobility was assessed by the Timed-Up-and-Go (TUG) test. Using pre-defined criteria, muscle weakness was considered as grip strength < 22 kg and poor mobility defined as TUG > 10.2 s. A subset of women had appendicular lean mass (ALM) determined by dual-energy X-ray absorptiometry at baseline and follow-up ($n = 261$). AAC_{sev} was evident in 193 (18.5%) women. Average decline in grip strength after 5 years was greater in those with AAC_{sev} than those without (3.6 ± 3.7 vs. 2.9 ± 4.2 kg; $p = 0.034$). This remained significant after adjustment for age, treatment allocation, diabetes, smoking history, renal function, medical record-derived prevalent vascular disease, BMI and physical activity ($\beta = -0.184$; 95% confidence interval: −0.361, −0.008; $p = 0.040$). AAC_{sev} was not associated with 5-year changes in TUG or ALM in univariable or multivariable analyses (all $p > 0.05$). In older women, severe aortic calcification was associated with greater 5-year decline in muscle strength, but not TUG or ALM. These findings support the concept that vascular disease may have an effect on the loss of muscular strength.

Keywords Aortic calcification · Physical function · Grip strength · Mobility · Older women

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Introduction

With advancing age, there is a progressive loss of muscle mass and function which promotes the onset of disability and increases the risk of falls and fractures [1]. Numerous factors are thought to promote this functional decline, including progressive worsening of co-morbidities such as diabetes and heart disease as well as lifestyle factors such as poor nutrient intake, smoking and reduced amounts of physical activity [2]. One area that has not been adequately described is the effects of vascular disease on the neuromuscular system.

Atherosclerotic vascular diseases also contribute to the development of functional decline. Calcification in the aorta is indicative of generalised atherosclerosis at other vascular beds and coronary artery calcification [3]. It is also associated with future cardiovascular events and deaths [4, 5]. Early abdominal aortic atherosclerotic lesions consisting of lipid-laden macrophages and vascular smooth muscle cells are common in adolescents and can either disappear or progress further to become more advanced atherosclerotic lesions [6]. Calcified abdominal aortic lesions are evidence of advanced atherosclerotic plaques that are easily visualised as raised areas by non-invasive imaging modalities [7]. Additionally, abdominal aortic calcification (AAC) may arise as a consequence of medial arteriosclerosis, or both processes can occur concurrently [8].

Epidemiological studies have reported that vascular calcification and musculoskeletal function are both predictive of fractures. Additionally, vascular calcification and musculoskeletal function may share common biological pathways [9]. The composition of calcified atherosclerotic lesions shares some features of bone. Similarly, the biological processes involved in vascular calcification share a number of features with age-related musculoskeletal decline such as decreased endothelial expression of the vitamin D receptor and downregulation of sclerostin in tissue [10, 11].

Recent studies implicate vascular disease as a contributor to age-related changes in muscle. A previous cross-sectional study of healthy older men and women demonstrated that the presence and severity of AAC was associated with low muscle mass [12]. Functional decline likely precedes and may even exceed rates of loss of muscle mass during ageing [13], but the association between AAC and physical function and decline is unknown. Previous observational studies of advanced atherosclerosis (such as carotid intima-media thickness and arterial stiffness) have shown that these surrogates of advanced atherosclerosis are higher in individuals with low handgrip strength [14] and that walking speeds and mobility decline with the presence of arterial plaques [15, 16]. However, it is unclear if AAC is a cause or consequence of functional decline based on these observations. We therefore sought to determine whether AAC measured at a single time point was associated with functional decline in a population of community-dwelling older women over 5 years.

Methods

This study was a secondary analysis of the Calcium Intake Fracture Outcome Study (CAIFOS) [17]. Participants in this study were originally recruited in 1998 for a 5-year, double-blind, randomised controlled trial (RCT) of daily calcium supplementation to prevent osteoporotic fracture, whose recruitment strategy has been detailed elsewhere [17]. Briefly, women aged 70 years and older were recruited from the general population in Western Australia. Of the 5586 women approached, 1500 were recruited into the study. All participants were ambulant, did not receive medication or have co-morbidities that could affect bone metabolism. Participants received 1.2 g of calcium carbonate daily or a matching placebo.

For the present study, participants who had AAC24 scores assessed from lateral spine dual-energy X-ray absorptiometry (DXA) scans at entry to the study at baseline in 1998 ($n=207$) or 1999 ($n=839$), and muscle strength and mobility assessed at baseline and the 5 year follow-up from their initial study visit in 2003, were included (total $n=1046$) (Fig. 1). All participants completed anthropometry and a validated food frequency questionnaire [18]. Creatinine was measured using an isotope dilution mass spectrometry (IDMS) traceable Jaffe kinetic assay on a Hitachi 917 analyzer (Roche Diagnostics GmbH, Mannheim Germany). Estimated glomerular filtration rate (eGFR) using creatinine and cystatin C was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [19]. Impaired renal function was defined as an eGFR < 60 mL/min/1.73 m^2. Prevalent atherosclerotic vascular disease (ASVD) was determined by atherosclerotic hospitalisations which were retrieved from the Western Australian Data Linkage System (WADLS) for each of the study participants. Prevalent atherosclerotic disease were defined using the principal Hospital discharge diagnosis codes with a look-back period of approximately 18 years depending on the date of clinic visit (1980 to date of clinical visit) from the International Classification of Diseases, Injuries and Causes of Death Clinical Modification (ICD-9-CM) [21]. These codes included ischemic heart disease (ICD-9-CM codes 410–414); heart failure (ICD-9-CM code 428); cerebrovascular disease excluding haemorrhage (ICD-9-CM codes 433–438); and peripheral arterial disease (ICD-9-CM codes 440–444). Diabetes status was determined by the medical

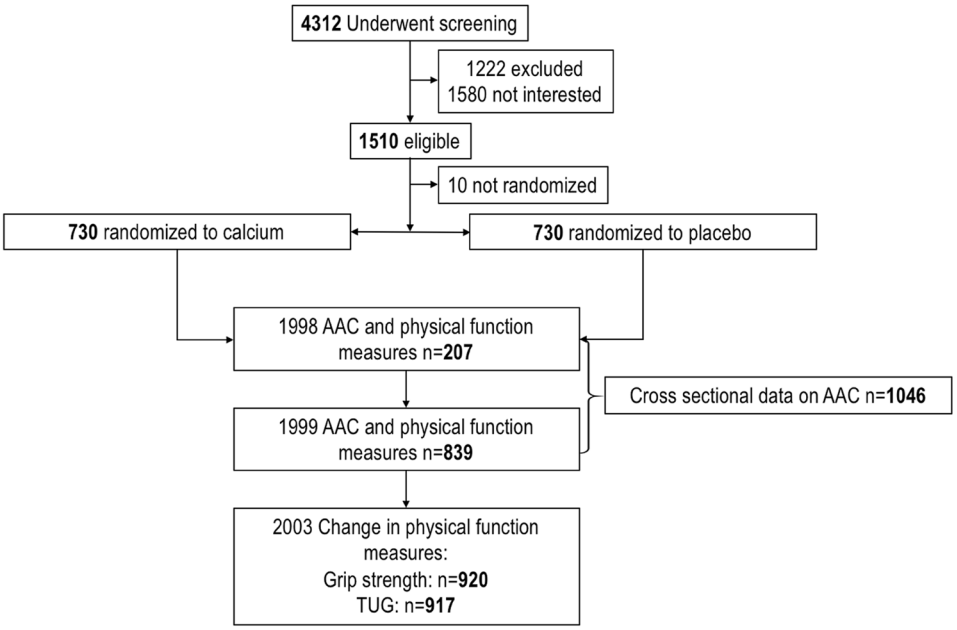

Fig. 1 Overview of the study design

history of study participants and verified by their primary care provider where possible. These data were coded using the International Classification of Primary Care—Plus (ICPC-Plus) method [20]. The coding methodology allows aggregation of different terms for similar pathologic entities as defined by the International Classification of Diseases and related Health Problems, 10th Revision (ICD-10) coding system. These data were then used to determine the presence of pre-existing diabetes (T89001-90009).

Hand grip strength was determined using a Jamar hand dynamometer (Lafayette Instrument Company, USA). Three repeated measures were taken for each hand and the highest recorded strength in the dominant hand was considered the maximum grip strength. Muscle weakness was defined as a maximum grip strength < 22 kg, as this threshold identified clinically relevant weakness in older women [21]. Mobility was assessed by the timed up and go (TUG) test, in which a participant was timed while rising from a chair, walking 3 m, turning and returning to sit on the chair. A TUG time > 10.2 s was considered to be slow, and was referred to as "mobility impairment". This threshold was previously shown to be predictive of fractures in older women [1]. Physical activity was assessed by a demographic questionnaire where participants reported their type of activity and hours per week to the question "Please list any sports recreation or regular physical activity, including walking, that you undertook in the last 3 months" [22]. The energy cost of such activities is given in METs (1 MET accounts for an individual's basal metabolic rate and equals ~ 1 kcal/kg/h). Activity levels (kcal/day) were calculated by multiplying frequency, duration, energy cost of the activities and the body weight of individuals [23]. Total cholesterol concentrations were determined using a Hitachi 917 auto analyser (Roche diagnostics). Plasma $25OHD_2$ and $25OHD_3$ concentrations were determined using a validated LC-MS/MS (Liquid Chromatography Tandem Mass Spectrometry) method at the RDDT Laboratories (Bundoora, VIC, Australia) according to published methodology and summed to obtained total plasma 25OHD concentration for each individual [24]. Between-run coefficients of variation (CVs) were 10.1% at a $25OHD_2$ mean concentration of 12 nmol/L and 11.3% at a $25OHD_3$ mean concentration of 60 nmol/L. These were categorised into normal (≥ 50 nmol/L), insufficient (< 50 nmol/L) and deficient (< 25 nmol/L). All AAC scores from 0 to 24 were derived from digitally enhanced lateral single-energy images of the thoraco-lumbar spine using a Hologic 4500A bone densitometer (Hologic, Bedford, MA, USA). A single experienced investigator (JTS) read all images using the validated semi quantitative scoring system [25]. The use of DXA to detect AAC has been validated against radiography where inter-class correlation coefficient between two readers on DXA was high (0.89: 0.80–0.94) and comparable to radiography (0.92; 0.88–0.95) [26]. Two other studies have shown similar agreement between methods [27, 28]. The AAC24 point system scores aortic calcification relative to each vertebral height (L1–L4) and is scored as 0 (no calcification), 1 (< one-third of the aortic wall), 2 (> one-third to two-thirds of the aortic wall) or 3 (> two-thirds of the aortic wall) for both the anterior and posterior aortic walls giving a maximum possible score of up to 24. Severity of AAC was also categorised using previously published groupings: low (AAC24 score 0 or 1); moderate (AAC24 score 2–5); and severe (AAC24 score > 5). AAC was categorised as not severe (AAC24 score ≤ 5) or severe (AAC24 score > 5). In those women who had AAC measured, 261 had appendicular lean mass (ALM) determined by whole-body

dual-energy X-ray absorptiometry (DXA) (Hologic, Bedford, MA, USA) at baseline and again at 5 years [29].

Statistical Analyses

Normally distributed variables were reported as mean ± standard deviation (SD), non-normally distributed variables were presented as median and interquartile range (IQR), while categorical variables were reported as frequency and percentage. Comparison of demographic, physical and clinical variables stratified by AAC severity was performed using *t* test, Mann–Whitney *U* test, χ^2 test or Mantel–Haenszel Chi-squared test for trend as appropriate to data distribution. Given that the aortic calcification score is not normally distributed, Spearman's rank correlation and age-adjusted partial correlation statistics were calculated for the correlation between calcification scores and functional measures, energy expenditure and anthropometric measures. Logistic regression models were constructed to determine if severe AAC was cross-sectionally associated with muscle weakness or mobility impairment at baseline. Linear regression models were constructed to determine if severe AAC was cross-sectionally associated with handgrip strength or TUG at baseline. Further, linear regression models were constructed to determine if severe AAC was associated with 5-year changes in handgrip strength or TUG. All regression models were constructed first as a minimally adjusted model controlling for age and treatment allocation and subsequently adjusted for body mass index (BMI) and relevant risk factors which included diabetes status, smoking status, ASVD, renal function and metabolic equivalents. As only a subset of women had ALM both at baseline and follow-up ($n=261$), these analyses were repeated in women with these measures stratified by skeletal muscle mass to determine if changes in physical function may be attributable to underlying conditions already affecting muscle mass. Low muscle mass was considered to be an ALM relative to BMI less than 0.512 in line with the Foundation for National Institute of Health (FNIH) definition of sarcopenia [30]. Regression coefficients are presented as the standard deviation increases/decreases in outcome associated with having severe AAC. All data were analysed using STATA v14.2 [StataCorp, 4905 Lakeway Dr College Station, TX, USA]. Values were considered statistically significant if $p<0.05$ and if the 95% confidence interval (95% CI) did not cross unity.

Results

Baseline data are shown in Table 1. Evidence of any calcification was seen in 762 (73%) of individuals and severe calcification (AAC24 score > 5) was evident in 193 (18%) individuals. Grip strength weakness, defined as maximum grip strength < 22 kg, was evident in 629 women (60.1%) and 32.6% had mobility impairment ($n=341$) defined as a TUG time > 10.2 s. Of those women with severe AAC, the frequency of allocation to calcium treatment was 45.6% ($n=88/193$) and this did not differ significantly ($p=0.331$) from those women with not severe AAC (49.4%; $n=422/853$). There were no differences in total cholesterol or vitamin D status amongst women with and without severe AAC.

Individuals with severe AAC were significantly older, had lower mean BMI, upper arm girth, triceps skin folds, and were more likely to be smokers, have ASVD, and use statins, low-dose aspirin, and any cardiovascular medication. Neither grip strength nor TUG time at baseline differed between those with and without severe AAC (Table 1). There were no significant correlations for AAC24 scores with baseline handgrip strength, TUG or ALM. AAC24 was negatively but weakly correlated with baseline BMI in an age-adjusted partial correlation model ($r=-0.067$; $p=0.030$) (Table 2).

One hundred and twenty-six women did not have grip strength recorded and 130 women did not have TUG recorded at follow-up. These women were slightly older (75.3 ± 2.8 vs. 74.8 ± 2.5 years; $p=0.052$) but were not heavier (BMI = 27.2 ± 5.1 vs. 27.1 ± 4.3 kg/m^2; $p=0.792$). In addition, women lost to follow-up had a lower baseline grip strength (19.7 ± 4.8 vs. 20.8 ± 4.7; $p=0.019$) and a slower baseline TUG (10.4 ± 2.9 vs. 9.5 ± 2.6; $p=0.005$). In women with follow-up functional measures, the median reduction in grip strength over 5 years was 3.0 kg (interquartile range: −5.5 to −0.75 kg; $n=920$). The average decline in grip strength in individuals with severe AAC (3.6 ± 3.7 kg) was greater than in those without (2.9 ± 4.2 kg) ($p=0.034$). The median increase in TUG times was 1.26 s (IQR: −0.02, 2.64; $n=917$). However, the average change in TUG times was similar between individuals with and without severe AAC. There were no significant correlations for AAC24 scores with change from baseline in handgrip strength or TUG (Table 2).

In minimally adjusted regression analyses controlling for age and treatment, and a fully adjusted model controlling for important risk factors, having severe AAC at baseline was associated with a greater decline in grip strength over 5 years (Table 3). Excluding outliers the results remained unchanged [standardised $\beta=-0.176$ (95% confidence interval: −0.337, −0.015) $p=0.032$]. After adjusting instead for upper arm girth (as a proxy for muscle mass in the arm), the association remained significant ($\beta=-0.187$; −0.363, −0.011; $p=0.037$). In a subgroup analysis including only women with ALM measurements and adjusting for ALM and not BMI, the association trended towards significance ($\beta=-0.226$; −0.487, 0.034; $p=0.088$) (Table 3). For women with a relative muscle mass above the FNIH threshold ($n=194$), AAC was associated with accelerated five-year

Table 1 Baseline demographic morphometric and functional characteristics

	All	AAC severity		*p* for difference
		Not severe (AAC24 ≤ 5)	Severe (AAC24 > 5)	
n (%)	1046	853 (81.6)	193 (18.4)	
Demographic data				
Age (years)	74.9 (2.6)	74.8 (2.5)	75.4 (2.7)	0.007
Smoker [*n* (%)]	373 (35.7)	289 (33.8)	84 (43.5)	0.032
Diabetes [*n* (%)]	61 (5.8)	51 (5.9)	10 (5.1)	0.669
ASVD [*n* (%)]	117 (11.2)	85 (9.9)	32 (16.5)	0.008
Antihypertensive use [*n* (%)]	449 (42.9)	357 (41.8)	92 (47.6)	0.140
Statin use (any) [*n* (%)]	198 (18.9)	135 (15.8)	63 (32.6)	< 0.001
Low-dose aspirin use [*n* (%)]	216 (20.6)	161 (18.8)	55 (28.5)	0.003
Any CV medication use [*n*(%)]	590 (56.4)	462 (54.1)	128 (66.3)	0.002
eGFR (mL/min/1.73 m^2)	66.9 (13.2)	66.9 (12.9)	66.6 (14.6)	0.694
Impaired renal function [*n*(%)]	294 (28.1)	230 (26.9)	64 (33.1)	0.084
Calcium treatment [*n* (%)]	510 (48.7)	422 (49.4)	88 (45.6)	0.331
Morphometric data				
Body mass index (BMI) (kg/m^2)	27.1 (4.4)	27.3 (4.6)	26.2 (3.6)	0.001
Appendicular lean mass (ALM) (kg) (*n* = 363)	14.9 (2.2)	14.9 (2.3)	14.8 (1.9)	0.711
Upper arm girth (cm)	32.6 (3.8)	32.8 (3.9)	32.0 (3.6)	0.013
Triceps skin fold (cm)	27.7 (8.3)	28.0 (8.5)	26.4 (7.5)	0.016
Biochemical data				
Total cholesterol (mg/dL) (*n* = 834)	226.1 (41.2)	225.9 (42.2)	226.7 (37.0)	0.825
Vitamin D status [*n* (%)]				
Deficient	34 (3.5)	27 (3.4)	7 (3.8)	0.398
Insufficient	233 (24.3)	184 (72.7)	49 (26.7)	
Normal	691 (72.1)	564 (72.7)	127 (69.4)	
Functional data				
Physical activity (kcal/kg/h)	147.1 (148.8)	147.4 (142.7)	145.9 (173.3)	0.902
Grip strength (kg)	20.7 (4.7)	20.6 (4.7)	20.7 (4.6)	0.801
Grip strength weakness [*n* (%)]	629 (60.1)	518 (60.7)	111 (57.5)	0.410
TUG (*s*)	9.7 (2.7)	9.7 (2.8)	9.4 (2.0)	0.165
Mobility impairment [*n* (%)]	341[32.6]	286 (33.5)	55 (28.5)	0.178

ASVD atherosclerotic vascular disease, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *TUG* timed up and go test

declines in handgrip strength (Table 4). Additional adjustment for vitamin D status at baseline did not alter findings (Supplementary Table 1). Additional adjustment for total cholesterol attenuated the regression coefficients and trended towards significance (Supplementary Table 1).

Discussion

In this longitudinal analysis of older women who participated in a randomised controlled trial of calcium supplementation on fracture outcomes, we determined that having severe aortic calcification (measured at a single time point) was associated with 5-year declines in grip strength after accounting for multiple co-morbidities. Interestingly, having severe AAC was not associated with 5-year declines in mobility or ALM. Overall, these findings suggest that detection of AAC in individuals, a robust indicator of cardiovascular disease and easily detectable on routine lateral spine imaging, may identify these individuals as being at a greater risk of muscle strength decline and thus may benefit from interventions to improve muscular strength. Interestingly, no association was evident regarding the association between AAC and ALM (likely due to low power) and this may suggest that any affects of AAC on muscular strength may be related more to neuromuscular factors and not muscle atrophy per se. Thus, it is unclear if vascular calcification has a direct or indirect effect, or both, on muscular strength. Aortic calcification promotes aortic stiffening which can lead to a multitude of adverse effects on peripheral blood

Table 2 Correlation of body composition and baseline functional measures with AAC as a continuous variable (AAC = 0–24)

	Spearman's rank correlation		Age-adjusted partial correlation	
	ρ	*p*	*r*	*p*
Baseline				
Body composition				
BMI (per SD)	−0.049	0.113	−0.067	0.030
Upper arm girth (per SD)	−0.027	0.376	−0.046	0.130
Triceps skin fold (per SD)	−0.011	0.712	−0.032	0.298
ALM at baseline (per SD) (*n* = 363)	−0.0293	0.577	−0.054	0.299
Functional measure				
Physical activity (per SD)	−0.006	0.835	0.005	0.865
Grip strength (per SD)	−0.007	0.818	0.015	0.609
TUG (per SD)	0.009	0.769	−0.043	0.159
Change from baseline				
Body composition				
Upper arm girth (per SD)	0.004	0.888	−0.011	0.731
Triceps skin fold (per SD)	−0.045	0.167	0.005	0.869
ALM (per SD) (*n* = 261)	−0.007	0.899	−0.067	0.276
Functional measure				
Grip strength (per SD) (n = 920)	−0.048	0.143	−0.055	0.094
TUG (per SD) (*n* = 917)	0.019	0.556	0.014	0.661

ALM appendicular lean mass, *BMI* body mass index, *SD* standard deviation, *TUG* timed up and go test

vessels and the neuromuscular system. In skeletal muscle, arteries supplying this tissue absorb most of the pulsatile energy content of propagating pressure and flow waveforms proximal to the capillaries. Sustained high central (aortic) stiffness reduces the protective stiffness gradients usually present between the heart and periphery and thus amplify the transfer of excessive, potentially harmful pulsatile energy into the periphery and tissues sensitive to high-flow and low-impedance such as the neuromuscular junction possibly impacting on efficient neuromuscular function [31]. Furthermore, occlusion of large vessels can restrict or diminish blood and thus nutrient supply to other conduit vessels hampering the proper functioning of limbs, resulting in functional decline [32]. Vascular calcification may be reflective of poor lifestyle behaviours and therefore physical decline may be inevitable but accelerated in these individuals. Other indirect factors such as circulating proteins regulating bone metabolism (for example sclerostin and Wnt signalling molecules), as well as inflammatory mediators (such as TNF-α and IL-6), may help explain the relationship demonstrated in this study as these factors are involved in both calcification and the loss of muscle mass and function [33–36]. We investigated a number of circulating factors including total cholesterol and also the vitamin D status of individuals. Adjustment for vitamin D status did not change the association; however, inclusion of cholesterol in analyses slightly attenuated the strength of the association and widened the confidence intervals, given the smaller sample size having data on cholesterol (*n* = 734–736/1046). Thus, these results may indicate a possibility of confounding by cholesterol, although there is no known direct physiologic connection between cholesterol and muscle strength, which would be needed to consider cholesterol a confounder. It is more likely the smaller sample size led to the slight reduction in statistical significance.

To our knowledge, no previous study has directly investigated the association of AAC and muscular strength. The present data support a previous study in older men (mean age at baseline approximately 77 years), in which greater carotid intima-media thickness (cIMT) at baseline was

Table 3 Associations between AAC severity (AAC ≥ 6 vs. < 6) and functional measure outcomes

Outcome measure	Model 1 β/Odds (95% CI)	*p*	Model 2 β/Odds (95% CI)	*p*
Baseline				
Grip strength (per SD)	0.062 (−0.091, 2.16)	0.424	0.079 (−0.080, 0.239)	0.331
Weak grip (yes/no)	0.823 (0.596, 1.134)	0.235	0.786 (0.558, 1.106)	0.167
TUG (per SD)	−0.143 (−0.298, 0.010)	0.068	−0.139 (−0.302, 0.022)	0.092
Slow TUG (yes/no)	0.746 (0.526, 1.058)	0.101	0.757 (0.519, 1.105)	0.150
ALM (per SD) (*n* = 363)	−0.032 (−0.285, 0.220)	0.801	0.140 (−0.083, 0.363)	0.219
Change from baseline				
Grip strength (per SD) (*n* = 920)	−0.178 (−0.345, −0.011)	0.037	−0.184 (−0.361, −0.008)	0.040
TUG (per SD) (*n* = 917)	−0.004 (−0.171, 0.163)	0.962	−0.012 (−0.187, 1.630)	0.891
ALM (per SD) (*n* = 261)	−0.102 (−3.670, 3.727)	0.988	0.003 (−0.271, 2.780)	0.980

Model 1 age & treatment, *2* age, treatment, BMI, smoking, ASVD, diabetes, eGFR & METS

ALM appendicular lean mass, *ASVD* atherosclerotic vascular disease, *BMI* body mass index, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *METS* metabolic equivalents, *TUG* timed up and go test

Table 4 Fully adjusted regression models of AAC severity (AAC ≥ 6 vs. < 6) functional measure outcomes stratified by relative muscle mass

Outcome measure	Normal relative muscle mass ($n = 194$) β/odds (95% CI)	p	Low relative muscle mass ($n = 67$) β/odds (95% CI)	p
Baseline				
Grip strength (per SD)	0.098 (−0.069, 0.267)	0.250	−0.085 (−0.602, 0.432)	0.744
Weak grip (yes/no)	0.763 (0.534, 1.090)	0.138	1.563(0.283, 8.613)	0.608
TUG (per SD)	−0.138 (−0.290, 0.013)	0.075	−0.017 (−1.018, 0.983)	0.973
Slow TUG (yes/no)	0.764 (0.512, 1.140)	0.188	0.579 (0.162, 2.057)	0.398
Change from baseline				
Grip strength (per SD)	−0.231 (−0.418, −0.044)	0.015	0.228 (−0.312, 0.770)	0.402
TUG (per SD)	−0.014 (−0.176, 0.147)	0.861	0.098 (−1.141, 1.338)	0.875

Adjusted for Age, treatment, BMI, smoking, ASVD, diabetes, eGFR & METS

ASVD atherosclerotic vascular disease, *BMI* body mass index, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *METS* metabolic equivalents, *TUG* timed up and go test

associated with lower handgrip strength at follow-up four years later [37]. The cIMT is a measure of atherosclerotic burden in the carotid artery and may represent both deposition of plaque on the intimal surface of the vascular wall as well as inflammatory and calcific infiltrates in the medial layer of the vascular wall [38]. No association was observed between cIMT and physical performance (determined by the short physical performance battery), or activities of daily living either at baseline or follow-up which aligns with observations from the present study. Further, despite reporting the change in cIMT from baseline to follow-up and having functional measures at baseline and follow-up, no data were reported on the association of changes in cIMT and changes in functional measures over time making it difficult to infer if worsening subclinical atherosclerosis parallels declines in physical function suggestive of a shared relationship. Another observational study of healthy middle-aged men and women (mean age approximately 47 years) has reported an inverse association between arm extensibility and the sit-and-reach test with cIMT [39]. In high-functioning middle-aged adults (mean age approximately 43 years), cIMT was higher in individuals in the lowest quartile of handgrip strength and systolic flow velocity (a measure of vessel resistance) [14]. Some literature, however, has reported no association between handgrip strength and atherosclerosis and thus the literature regarding the possible effect of vascular calcification and atherosclerosis on physical function is mixed [40]. It is interesting to note that the mean age of participants in studies reporting poor physical function as a risk factor for ASVD appears to be substantially lower than in studies reporting prevalent ASVD as a risk factor for poor physical function. That is to say that the effects of physical function on ASVD appear to become less pronounced over time (i.e. physical function contributes more to vascular risk in middle age and that in older age, prevalent vascular disease contributes to functional decline). This concept is supported by studies in autopsies of individuals 2–15 years old which have revealed that the prevalence of fibrotic/atherosclerotic lesions is as high as 20% [41]. The effects of these lesions in early life would likely accumulate such that small decrements in blood supply and sustained central stiffness impacting on neuromuscular function throughout the life course may manifest as clinically relevant functional deficits in middle age. At this point, a vicious cycle would likely ensue in which poor physical function would promote further vascular deterioration from an inability/difficulty in performing a sufficient amounts of physical exertion in a manner that would favourably evoke endothelial cell nitric oxide production, inhibit sympathetic nerve activity and ultimately allow for adequate tissue perfusion [42, 43]. Manifest vascular disease has already been demonstrated to negatively impact physical fitness and exercise capacity [44]. This may promote the progression of subclinical vascular disease to overt, clinically significant macrovascular disease due to a lack of physical activity from compromised cardio-respiratory fitness.

A previous study demonstrated that calcification in the coronary artery was associated with 9-year declines in walking speeds in older adults (mean age approximately 62 years), and in another study of older adults (mean age approximately 73 years) free of known cardiovascular disease, carotid plaque burden was associated with greater 12-month increases in TUG [15, 16]. However, in the present study we observed no association between AAC and TUG times as a continuous variable or between AAC and having mobility impairment (a TUG time > 10.2 s) at baseline or at follow-up. Also, AAC was not a significant predictor of 5-year changes in TUG. Associations of AAC may be more closely related to more discrete assessments of muscle function such as handgrip strength which involves markedly fewer muscle groups and less neuromuscular involvement.

Individuals in the present study, while not having sustained a clinical cardiovascular event, were likely to have subclinical cardiovascular disease as evidenced by the relatively high prevalence of cardio-protective medications. Exercise is commonly recommended in those with identified cardiovascular disease as part of disease management. Exercise, particularly resistance training, has proven benefits in improving muscular strength and physical function in all age groups and is safe and effective in the elderly frail [45]. Thus, those with identified AAC may benefit from muscular strength training to both improve cardiovascular risk and prevent functional decline. In a previous study, but not in this study, we identified a cross-sectional relationship between AAC severity and low relative muscle mass [12]. In this study, lean muscle mass was only available in a small subset which may have reduced power to have detected a significant association. Nevertheless, these data demonstrate that AAC may be independently related to muscle mass and function.

There are a number of important limitations to this study that must be considered when interpreting the results. Firstly, as this was an observational study, we cannot infer causality. Secondly, this study was limited by measurement of calcification at only one time point. Given an association between AAC and changes in handgrip strength was evident, it may be more informative to determine if changes in calcification correlate with changes in physical function. Given the advanced age of this cohort, it is likely that aortic calcification is already well established. Thirdly, the participants in this cohort were Caucasian women aged over 70 years and thus the results may not be generalisable to older men and non-Caucasian populations. Therefore, longitudinal analyses conducted in cohorts of men and women at an earlier age are needed to investigate if functional decline precedes the development/progression of AAC or vice versa. This is particularly important as men and women have different profiles of functional decline and cardiovascular risk during ageing. Fourth, other performance assessments, such as the 400-m walk test, may assist in clarifying the association between AAC and physical function. Fifth, DXA, while a useful tool to determine body composition, does not adequately separate out non-muscle contributors to lean mass such as fibrous tissue and water and is probably best suited to determining fat mass. Finally, we only observed modest and inconsistent associations between AAC and functional measures meaning our findings should be interpreted cautiously particularly considering some women were lost to follow-up. These women had poorer baseline functional measures meaning that we may have underestimated the true effect in this population.

In conclusion, older women with severe AAC experienced decline in handgrip strength, a measure of muscular weakness, independent of established risk factors. As such, this study supports other evidence for a potential muscle function–vascular calcification relationship. Women identified to have severe AAC may be at risk of functional decline and thus may also likely benefit from interventions aimed at promoting physical function. Future studies with longitudinal measures of AAC and comprehensive muscle phenotypes are needed to elucidate potential mechanisms. These studies should include both men and women to validate these findings.

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Author Contributions AJR: Study concept and design, data analysis, interpretation of data and manuscript preparation. JRL: Interpretation of data and manuscript preparation. DSS: Interpretation of data and manuscript preparation. DPK: Interpretation of data and manuscript preparation. JTS: Acquisition of data, interpretation of data and manuscript preparation. PRE: Interpretation of data and manuscript preparation. RLP: Study concept and design, acquisition of data, interpretation of data and manuscript preparation.

Compliance with Ethical Standards

Conflict of interest Alexander J. Rodríguez, Joshua R. Lewis, David S. Scott, Douglas P. Kiel, John T. Schousboe, Peter R. Ebeling and Richard L. Prince declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent Trial registration: Australian New Zealand Clinical Trials Registry ACTRN12615000750583. The study conformed to all ethical requirements according to the Human Research Ethics Committee of the Western Australian Department of Health (DOHWA HREC), project number #2009/24. All participants gave informed consent.

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