Preventive Medicine Reports 51 (2025) 102994

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Analysis of the relationship between abdominal aortic calcification and frailty in the middle-aged and older US population

Rena Rehemuding [a,1], Kaisaierjiang Kadier [a,1], Xinliang Peng [a,1], Pengfei Liu [a], Diliyaer Dilixiati [b], Aikeliyaer Ainiwaer [c], Xiaozhu Liu [d], Xiangtao Liu [e,*], Xiang Ma [a,**]

[a] Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China
[b] Department of Urology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China
[c] Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands
[d] Emergency and Critical Care Medical Center, Beijing Shijitan Hospital, Capital Medical University, Beijing, China
[e] College of Medical Engineering and Technology, Xinjiang Medical University, Urumqi, China

ARTICLE INFO

Keywords:
Abdominal aortic calcification
Frailty
National Health and nutrition examination survey
Population health

ABSTRACT

Background and Objective: Abdominal aortic calcification (AAC) is a marker of cardiovascular disease and is associated with increased mortality in middle-aged and older populations. However, its relationship with frailty remains unclear.

Methods: Data were obtained from the 2013–2014 National Health and Nutrition Examination Survey. AAC was quantified using the Kauppila scoring system based on dual-energy X-ray absorptiometry. Frailty was assessed using the frailty index. Multivariable logistic regression models examined the association between AAC and frailty.

Results: A total of 2987 adults aged ≥40 years were included. Compared to individuals with an AAC-8 score of 0, low-risk (AAC-8 score = 1–2; OR: 1.24; 95 % CI, 1.00–1.53) and high-risk AAC (AAC-8 score ≥ 3; OR: 1.83; 95 % CI, 1.03–3.23) were associated with higher odds of frailty. Similarly, mild to moderate AAC (0 < AAC-24 score ≤ 6; OR: 1.26; 95 % CI, 1.03–1.54) and severe AAC (AAC-24 score > 6; OR: 1.79; 95 % CI, 1.07–2.99) showed positive associations with frailty.

Conclusions: Among middle-aged and older populations in the United States, there exists a positive correlation between AAC and frailty. Our findings suggest that the AAC score holds promise as a valuable tool for the early identification of frailty.

1. Introduction

The rise in life expectancy is invariably linked to an increase in chronic diseases and frailty, significantly impacting healthcare systems (Fan et al., 2020; Hoogendijk et al., 2019). Frailty is characterized by a decline in physiological system function, deterioration in physiological reserve, and impaired ability to maintain homeostasis. It is closely associated with the degeneration of the sensory, nervous, and musculoskeletal systems, resulting in an increased susceptibility to adverse effects from stressors (Hoogendijk et al., 2019; Dent et al., 2024). Substantial evidence indicates that frailty is linked to unfavorable health outcomes, such as falls, disability, and mortality (Hanlon et al., 2018; Si et al., 2021). Due to the varied and subjective nature of frailty in clinical presentations, precise quantification of frailty serves as a valuable indicator of personal health status (Dent et al., 2019). The most important frailty measurement tools currently include frailty index and frail phenotype (Blodgett et al., 2015; Mitnitski et al., 2001; Searle et al., 2008). Recently, there has been a heightened focus on the link between

Abbreviations: CVD, cardiovascular disease; AAC, abdominal aortic calcification; DXA, dual-energy X-ray absorptiometry; NHANES, National Health and Nutrition Examination Survey; PIR, poverty-income ratio; FHCVD, family history of cardiovascular disease; CKD, chronic kidney disease; SD, standard deviation; 95 % CI, 95 % confidence interval; ORs, odds ratios; VIF, variance inflation factor;.

* **Correspondence to:** College of Medical Engineering and Technology, Xinjiang Medical University, Shangde North Road No. 567, Urumqi 830017, China.
** **Correspondence to:** Department of Cardiology, First Affiliated Hospital of Xinjiang Medical University, Xinyi Road No. 393, Urumqi 830054, China.
E-mail addresses: liu_xt005@xjmu.edu.cn (X. Liu), maxiangxj@yeah.net (X. Ma).
[1] These authors have contributed equally to this work and share first authorship

https://doi.org/10.1016/j.pmedr.2025.102994
Received 25 September 2024; Received in revised form 26 January 2025; Accepted 27 January 2025
Available online 1 February 2025

cardiovascular disease (CVD) and frailty, driven by the recognition that the aging process accelerates the emergence and evolution of age-related illnesses (Damluji et al., 2021).

Abdominal aortic calcification (AAC) serves as a valuable indicator for assessing the extent of subclinical atherosclerosis and is a reliable predictor of morbidity and mortality in CVD (Wilson et al., 2001; Górriz et al., 2015; Yang et al., 2021). Simultaneously, research has demonstrated that AAC is linked to declining grip strength (Ramírez-Vélez et al., 2021), impaired cognitive function (Wei et al., 2021), increased risk of dementia in later life (Porter et al., 2022), and rapid weight loss (Smith et al., 2024) among middle-aged and older individuals. Based on the evidence presented in the aforementioned studies, it is plausible that AAC could serve as a predictive marker for frailty. In a cross-sectional community-based study involving older adults, the presence of AAC was shown to be correlated with both prefrailty and frailty, exhibiting a dose-response relationship (Lee et al., 2020).

Kauppila et al. employed lateral lumbar radiographs as a tool for grading AAC and illustrated its effectiveness in longitudinal cohort studies spanning up to 25 years (Kauppila et al., 1997). According to the AAC score, subclinical vascular disease can be evaluated inexpensively and has independent predictive value compared to coronary artery calcification for cardiovascular events and mortality (Criqui et al., 2014). With the widespread clinical application of dual-energy X-ray absorptiometry (DXA), the simultaneous measurement of AAC scores represents a potentially innovative and non-invasive approach to identifying middle-aged and older populations vulnerable to frailty. This study utilized data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) to investigate the association between AAC and frailty among middle-aged and older adults in the United States, aiming to offer novel perspectives for clinical screening and the prevention of frailty.

2. Materials and methods

2.1. Study population

The study population was obtained from the NHANES database for the 2013–2014 survey period. NHANES is a research program administered by the Centers for Disease Control and Prevention to evaluate the health and nutritional status of individuals of all ages throughout the United States. The data collection encompasses a broad range of items, such as questionnaires, examination and laboratory parameters. Additionally, a multistage complex sampling design is employed to ensure that the sample is nationally representative (Johnson et al., 2014).

The NHANES 2013–2014 was the only cycle in which AAC was examined by DXA in participants over 40 years of age. During this survey cycle, a total of 10,175 participants were included. Our study excluded 6360 participants who were under 40 years of age, and an additional 828 participants were excluded due to missing AAC scores and insufficient items to assess frailty. The final number of subjects included in this study's sample was 2987 (Fig. 1). **Supplementary Table 1** outlines the characteristics of participants who were excluded from this study due to missing data. All participants provided written informed consent to participate in the study to the NHANES project team and received approval from the NCHS Research Ethics Review Board. The study adhered to the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology for reporting cross-sectional studies (von Elm et al., 2007), with all procedures conducted in accordance with the principles outlined in the 1975 Declaration of Helsinki.

2.2. Definition of AAC

In this study, the exposure variable examined was AAC, which was assessed using dual-energy X-ray absorptiometry (DXA) based on lateral spine images of the lumbar vertebrae L1–L4. DXA scans were performed by trained and certified radiology technologists from the University of California, San Francisco. The analysis was conducted using the Optasia SpinAnalyzer software, and all images were interpreted and scored according to standardized protocols. The NHANES database provided evaluated results for both AAC-24 and AAC-8 scoring systems. The detection of AAC in lateral lumbar spine images by DXA demonstrated high specificity and sensitivity at a low radiation dose and was both inexpensive and convenient (Schousboe et al., 2017). AAC scores, specifically AAC-24 and AAC-8, were calculated using the Kauppila scoring method (Kauppila et al., 1997). Individuals under 40 years of age, pregnant, weighing over 450 pounds, or who had ingested barium within the past week were not eligible to undergo a DXA scan for the assessment of AAC in the NHANES examination. Consequently, the data pertaining to these individuals were deemed missing and excluded from the study. The degree of AAC was ascertained by categorizing the AAC-24 score and AAC-8 score based on thresholds established in prior research studies (Ramírez-Vélez et al., 2021; Wei et al., 2021; Kauppila et al., 1997; Kadier et al., 2023). The AAC-8 scores were categorized into two groups: no calcification (AAC-8 score = 0), the low-risk group (AAC-8 score = 1–2) and the high-risk group (AAC-8 score $\geq$ 3). Additionally, the AAC-24 scores were classified into three groups: no calcification (AAC-24 score = 0), mild to moderate calcification (0 < AAC-24 score $\leq$ 6), and severe calcification (AAC-24 score > 6). A detailed comparison between the AAC-24 and AAC-8 scores can be found in Table 1.

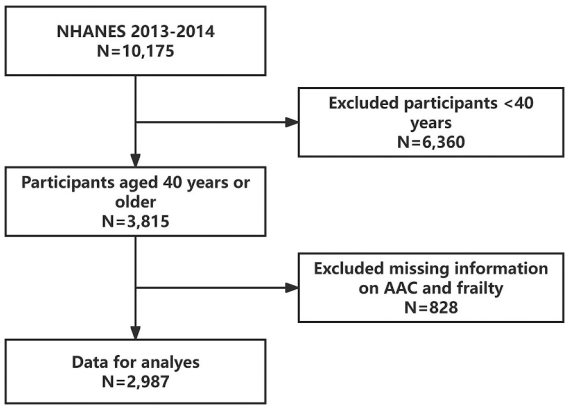

FIG. 1. Flow chart of eligible National Health and Nutrition Examination Survey participants included in this study.

2.3. Assessment of frailty

Frailty was the primary outcome in this study, and it was evaluated using the frailty index. Prior research has developed frailty index comprising 49 diagnostic criteria derived from the NHANES database (Hakeem et al., 2021), following the established procedure of the Searle

Table 1
Detailed Comparison of abdominal aortic calcification-8 and abdominal aortic calcification-24 Scoring Systems.

	AAC-8	AAC-24
Segments Evaluated	Anterior and posterior aortic walls in front of L1-L4 as a whole	Anterior and posterior aortic walls divided into 8 segments across L1-L4
Scoring Range	0 to 8 (0 to 4 for anterior and posterior)	0 to 24 (0–3 per segment)
Scoring Method	Based on total calcification length relative to vertebral height	Based on proportion of calcified area per segment
Risk Classification	No calcification (0), Low-risk (1–2), High-risk ($\geq$3)	No calcification (0), Mild to Moderate (1–6), Severe (>6)
Advantages	Short assessment time	High reliability

Abbreviations: AAC, abdominal aortic calcification.

team for constructing frailty index (Searle et al., 2008). These diagnostic items encompass cognition, functional dependence, depressive symptoms, comorbidities, medication use, physical assessments, and laboratory tests. Scores ranging from 0 to 1 were assigned based on the severity of the deficit, and the frailty index was calculated by dividing the total score by the number of items answered. In order to maintain the accuracy of frailty diagnosis, only participants who completed a minimum of 30 items were included in this study (Searle et al., 2008). Detailed information regarding the variables of the frailty index and their corresponding scoring criteria can be found in **Supplementary Table 2**. Frailty was defined as a frailty index exceeding 0.21 (Blodgett et al., 2015; Jiang et al., 2023).

2.4. Covariates

In order to mitigate the impact of confounding variables, we incorporated established covariates based on prior research findings (Kadier et al., 2023; Hakeem et al., 2021; Jiang et al., 2023). The covariates encompassed in the study comprised age, sex, race, education, marital status, insurance status, poverty-income ratio (PIR), smoking, alcohol consumption status, family history of cardiovascular disease (FHCVD), diabetes, chronic kidney disease (CKD) and 25-hydroxyvitamin D. Trained NHANES interviewers used a computer-assisted system to collect the aforementioned information during home interviews. Socioeconomic factors were assessed and collected during home interviews, with PIR categorized into three groups: <1.3, 1.3–3.5, and $>$ 3.5. Lower PIR was observed to be associated with higher levels of poverty. Behavioral factors were obtained through self-reports, with smoking status classified into never smokers (individuals who have never smoked more than 100 cigarettes in their lifetime), former smokers (those who have smoked more than 100 cigarettes in their lifetime but have since quit), and current smokers (individuals who have smoked at least 100 cigarettes in their lifetime and continue to smoke on some days or every day). Alcohol consumption was categorized as never drinkers (individuals who consumed <12 drinks in their lifetime), former drinkers (those who had ≥ 12 drinks in 1 year but did not drink in the last year, or did not drink in the last year but consumed ≥ 12 drinks in their lifetime), current mild-to-moderate drinkers (≤ 1 drink per day for women or ≤ 2 drinks per day for men on average over the past year), and current heavier drinkers (>1 drink per day for women or > 2 drinks per day for men on average over the past year). Participants who self-reported a medical diagnosis of heart failure, angina, coronary heart disease, heart attack, or stroke, as confirmed by a physician, were categorized as having CVD (For sensitivity analysis only). A FHCVD was defined as having been informed by a healthcare professional that a close biological relative experienced a heart attack or angina before the age of 50. Diabetes was defined as a diagnosis made by a physician or other healthcare professional, glycated hemoglobin (%) greater than 6.5, random blood glucose (mmol/L) equal to or greater than 11.1, or use of diabetes medication or insulin. As defined by the International Renal Association, CKD is characterized by an estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or a urine albumin–creatinine ratio of at least 30. Based on serum creatinine, the CKD Epidemiology Collaboration equation was used to estimate the glomerular filtration rate. The NHANES collaborative laboratory utilized ultra-high performance liquid chromatography-tandem mass spectrometry to perform the quantitative analysis of 25-hydroxyvitamin D in human serum.

2.5. Statistical analysis

All statistical analyses conducted in this study adhered to the NHANES complex sampling design, incorporating survey design variables and sampling weights to extend the findings to the broader US population (Johnson et al., 2014). All results of this study were weighted by 2- year MEC weights.

Descriptive statistics were reported as mean ± standard deviation (SD) or median (IQR) for continuous variables and as weighted percentage (95 % confidence interval, 95 % CI) for categorical variables. Continuous variables were compared between groups using the *t*-test or Mann-Whitney *U* test, while the Rao-Scott chi-square test was employed for comparing categorical variables across groups. Multivariable logistic regression analysis was utilized to examine the relationship between AAC and frailty, calculating odds ratios (ORs) and 95 % CI. Mode 1 represents the unadjusted model, while Model 2 was adjusted for age, sex, and race. Model 3 incorporated adjustments for all covariates considered in the study [age (40–59 and ≥ 60), sex (Male and Female), race (Mexican American, non-Hispanic White, non-Hispanic Black, and Others), marital status (Married/Living with Partner, Widowed/ Divorced/ Separated and Never married), education (Less than high school, High school and Above high school), PIR (<1.3, 1.3–3.5 and $>$ 3.5), insurance coverage status (Yes and No), Smoking (Never, Former and Now), alcohol consumption status (Never, Former, Mild-Moderate and Heavy), FHCVD (Yes and No), diabetes (Yes and No), CKD (Yes and No) and total 25-hydroxyvitamin D (Continuous)]. Additionally, we assessed the variance inflation factor (VIF) for each covariate and observed that all VIF values were below 5, indicating the absence of significant multicollinearity among the covariates.

In this study, missing values for both continuous and categorical covariates were imputed using the MissForest package, a popular imputation method in statistical analysis (Stekhoven and Bühlmann, 2012). **Supplementary Table 3** presents the counts and proportions of missing data for the covariates. Sensitivity analyses were performed according to the following criteria: (1) inclusion of only participants with complete covariate data; (2) exclusion of participants with CVD; (3) define frailty using more stringent thresholds (frailty index ≥ 0.25) (Fan et al., 2020); and (4) analysis conducted using uncomplicated sampling procedures.The statistical analysis was carried out using R software (version 4.1.3; https://www.R-Project.org), utilizing complex sampling modules. Statistical significance was determined by *P*-values below 0.05 in all two-sided tests performed for the analyses.

3. Results

3.1. Baseline characteristics

This study included 2987 participants aged over 40 years, corresponding to a population of 120,166,483 noninstitutionalized residents in the United States within the same age group. Table 2 presents the baseline characteristics of participants categorized by frailty. In general, the participants had a mean age ± SD of 57.8 ± 0.3 years, with 52.2 % (95 % CI 46.4 to 58.0) being female and 71.9 % (95 % CI 58.0 to 85.8) identifying as non-Hispanic white. The median AAC-8 and AAC-24 scores within the study population were observed to be 0 (IQR: 0–1) and 0 (IQR: 0–2), respectively. The prevalence of high-risk AAC (AAC-8 score ≥ 3) and severe AAC (AAC-24 score > 6) were 8.0 % (95 % CI 6.5 to 9.6) and 8.0 % (95 % CI 6.7 to 9.3), respectively. Simultaneously, individuals classified as frail tended to be older and exhibited significantly higher proportions of females, lower educational attainment, lower PIR, and higher proportions of current or former tobacco users, alcohol consumers, and comorbidities such as CVD, diabetes, and CKD compared to their non-frail counterparts. Of particular note, there was a notable rise in the prevalence of AAC among this group.

Baseline results categorized based on the presence or absence of AAC are provided in **Supplementary Table 4**. The findings indicated a population prevalence of 23.0 % (95 % CI 20.7 to 25.4) for frailty, with a particularly high prevalence observed among individuals diagnosed with AAC. Meanwhile, as the severity of AAC increased, variations in age, race, marital status, education, PIR, insurance status, smoking, alcohol consumption, CVD, diabetes, CKD and total 25-hydroxyvitamin D were observed. And strong concordance was observed between the AAC-8 and AAC-24 scores.

Table 2
General characteristics of the included participants ($n = 2987$) in the National Health and Nutrition Examination Survey 2013–2014.

Characters	Overall (n = 2987)	Non-frailty ($n = 2192$)	Frailty[a] ($n = 795$)	*P* value
Age, year	57.8 ± 0.3	56.8 ± 0.3	61.1 ± 0.5	< 0.01
Age, year				< 0.01
40–59	58.0 (50.5,65.5)	60.6 (57.4,63.8)	49.2 (45.5,53.0)	
≥ 60	42.0 (36.6,47.5)	39.4 (36.2,42.6)	50.8 (47.0,54.5)	
Sex				< 0.01
Male	47.8 (41.4,54.2)	51.6 (49.8,53.5)	35.0 (31.2,38.8)	
Female	52.2 (46.4,58.0)	48.4 (46.5,50.2)	65.0 (61.2,68.8)	
Race				< 0.01
Mexican American	6.8(3.9, 9.8)	6.7(3.6, 9.8)	7.4 (3.5,11.2)	
Non-Hispanic Black	10.0 (8.2,11.7)	8.8 (6.2,11.3)	14.1 (11.1,17.0)	
Non-Hispanic White	71.9 (58.0,85.8)	73.0 (66.8,79.3)	68.0 (62.1,74.0)	
Others	11.3 (9.6,13.0)	11.5 (9.2,13.9)	10.5 (7.3,13.7)	
Marital				< 0.01
Married/Living with Partner	68.4 (58.8,77.9)	71.9 (69.5,74.4)	56.7 (52.5,60.8)	
Widowed/Divorced/ Separated	24.7 (21.4,27.9)	21.2 (19.3,23.1)	36.3 (32.0,40.5)	
Never married	6.9(6.0, 7.8)	6.9(5.5,8.3)	7.1(5.1,9.0)	
Education				< 0.01
Less than high school	15.2 (12.2,18.2)	12.8 (9.5,16.2)	23.1 (18.6,27.6)	
High school	21.8 (17.7,25.9)	20.5 (17.2,23.8)	26.0 (22.7,29.3)	
Above high school	63.0 (52.6,73.4)	66.6 (61.0,72.2)	50.9 (45.5,56.2)	
Poverty-income ratio				< 0.01
< 1.3	18.3 (13.7,22.9)	14.8 (11.0,18.6)	30.0 (23.1,36.8)	
1.3–3.5	37.6 (33.6,41.5)	35.8 (33.0,38.7)	43.3 (38.5,48.0)	
> 3.5	44.1 (35.4,52.9)	49.3 (43.8,54.9)	26.8 (22.9,30.6)	
Insurance, yes	87.6 (76.1,99.0)	87.0 (84.2,89.7)	89.7 (87.4,92.0)	0.06
Smoking status				< 0.01
Never	54.2 (47.0,61.4)	58.4 (55.1,61.8)	40.1 (36.1,44.1)	
Former	28.3 (23.3,33.3)	27.0 (24.1,30.0)	32.5 (29.1,35.9)	
Now	17.5 (14.4,20.6)	14.5 (12.4,16.6)	27.4 (22.2,32.6)	
Alcohol consumption status				< 0.01
Never	11.5 (8.3,14.7)	11.1 (8.2,14.0)	13.1 (9.4,16.8)	
Former	17.5 (14.5,20.6)	15.0 (12.7,17.2)	26.2 (21.9,30.6)	
Mild-Moderate	40.0 (33.7,46.3)	41.7 (38.1,45.2)	34.5 (28.3,40.6)	
Heavy	30.9 (26.6,35.2)	32.3 (30.3,34.4)	26.2 (22.0,30.5)	0.03
FHCVD, yes	14.0 (10.8,17.1)	12.8 (10.5,15.1)	17.9 (13.3,22.5)	0.03
CVD, yes	11.4 (9.6,13.1)	5.8(4.8, 6.8)	30.0 (26.4,33.7)	< 0.01
Diabetes, yes	16.4 (14.4,18.5)	10.8 (9.0,12.6)	35.3 (31.4,39.1)	< 0.01
CKD, yes	19.1 (17.3,21.0)	15.0 (12.8,17.2)	33.0 (28.0,38.0)	< 0.01
Total 25-hydroxyvitamin D (nmol/L)	75.3 ± 1.4	75.7 ± 1.4	73.9 ± 1.6	0.17
AAC-8 score	0(0–1)	0(0–1)	0(0–2)	< 0.01
AAC-8 score				< 0.01
0	70.7 (61.4,80.0)	73.7 (70.3,77.2)	60.5 (57.3,63.7)	
1–2	21.3 (17.7,24.8)	20.5 (17.6,23.5)	23.7 (20.8,26.7)	
≥3	8.0(6.5, 9.6)	5.7(4.5, 6.9)	15.8 (11.8,19.8)	
AAC-24 score	0(0–2)	0(0–1)	0(0–4)	< 0.01
AAC-24 score				< 0.01
0	70.7 (61.3,80.0)	73.7 (70.3,77.2)	60.3 (57.2,63.5)	
0–6	21.3 (17.5,25.2)	20.5 (17.8,23.2)	24.2 (20.3,28.0)	
> 6	8.0(6.7, 9.3)	5.8(4.7, 6.8)	15.5 (11.8,19.1)	

Abbreviations: FHCVD, Family history of cardiovascular disease; CVD, Cardiovascular disease; CKD, Chronic kidney disease; AAC, abdominal aortic calcification.
Continuous variables were presented as mean ± standard deviation or median (IQR), depending on their distribution, and comparisons were performed using *t*-test or Mann-Whitney *U* test.
Categorical variables are presented as weighted percentages (95 % confidence interval), and were compared using the weighted Rao-Scott chi-square test.
[a] frailty was defined as a frailty index exceeding 0.21.

3.2. Association between AAC and frailty

Table 3 presents the weighted multivariable logistic regression analysis results, illustrating the correlation between AAC and frailty. In fully adjusted Model 3, the ORs for frailty was 1.15(95 % CI 1.04–1.26) for each 1-point increase in AAC-8 score. And the ORs for frailty was 1.05 (95 % CI 1.02–1.09) for each 1-point increase in AAC-24 score. In the results categorized by AAC-8 score, the high-risk AAC individuals with AAC-8 score ≥ 3 had a higher odds of frailty compared with those with AAC-8 score = 0 (OR: 1.83; 95 % CI, 1.03–3.23). Compared with participants without AAC (AAC-24 score = 0) as a reference, both mild to moderate AAC (0 < AAC-24 score ≤ 6) and severe AAC (AAC-24 score > 6) showed a positive association with an increased prevalence of frailty, with the ORs and 95 % CIs of 1.26(1.03–1.54) and 1.79 (1.07,2.99), respectively.

3.3. Sensitivity analyses

Supplementary Table 5 presents the results of the sensitivity analyses conducted in this study. The analysis using the non-weighted model yielded results consistent with the primary analysis, further supporting the relative robustness of the findings. However, when participants with CVD and those with missing covariates were excluded, the association disappeared. Possible explanations include the fact that most participants with CVD also had AAC, and the exclusion of individuals with missing covariates reduced the sample size, thereby diminishing statistical power. Additionally, when frailty was defined using a more stringent threshold (frailty index ≥0.25), the association with frailty was observed only in the severe AAC group.

Table 3
Weighted multivariable logistic regression coefficients and 95 % confidence interval for the association between abdominal aortic calcification and frailty[a] in the middle-aged and older population: The National Health and Nutrition Examination Survey, United States of America, 2013–2014.

	Case/ participants	Model 1	Model 2	Model 3
		OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
AAC-8 score				
Continuous	795/2987	1.32 (1.22,1.42)	1.29 (1.17,1.43)	1.15 (1.04,1.26)
0	482/2068	1.00	1.00	1.00
1–2	186/638	1.41 (1.15,1.73)	1.40 (1.13,1.75)	1.24 (1.00,1.53)
≥3	127/281	3.37 (2.28,4.97)	3.09 (1.87,5.12)	1.83 (1.03,3.23)
AAC-24 score				
Continuous	795/2987	1.11 (1.08,1.14)	1.10 (1.07,1.14)	1.05 (1.02,1.09)
0	481/2067	1.00	1.00	1.00
0–6	188/638	1.44 (1.19,1.75)	1.44 (1.16,1.79)	1.26 (1.03,1.54)
>6	126/282	3.28 (2.36,4.55)	3.04 (1.94,4.77)	1.79 (1.07,2.99)

Abbreviation: AAC, abdominal aortic calcification; OR, odds ratios; 95 % CI, 95 % confidence interval.
Model 1: Unadjusted.
Model 2: Adjusted for age, sex, and race.
Model 3: Adjusted for age, sex, race, education, marital status, PIR, insurance status, smoking status, alcohol consumption status, FHCVD, diabetes, CKD and total 25-hydroxyvitamin D.
[a] frailty was defined as a frailty index exceeding 0.21.

4. Discussion

To the best of our knowledge, this study represents the inaugural investigation into the relationship between AAC and frailty within a cross-sectional, nationally representative study. Notably, this exploration utilized the AAC scoring system in tandem with a frailty index. Our study comprehensively considered participants' socio-economic status and behavioral factors while controlling for a diverse array of confounding variables. The findings indicate a positive correlation between AAC and frailty, as delineated by both AAC-8 and AAC-24. In sensitivity analyses, the findings exhibited a considerable degree of robustness.

The potential association between frailty and CVD underscores the importance of promptly detecting frailty status for patient prognosis. Frailty has emerged as a notable risk factor for the occurrence of major adverse cardiovascular events, as evidenced by findings from the National Health and Aging Trends Study (Damluji et al., 2021). Concurrently, research conducted among US veterans indicates that frail individuals face elevated risks of cardiovascular mortality, as well as heightened incidences of myocardial infarction and stroke (Shrauner et al., 2022). However, it is fortunate that reversing frailty status reduces the risk of developing cardiovascular events (He et al., 2024), necessitating early detection of frailty status and prompt intervention. AAC serves as a dependable predictor of both morbidity and mortality in CVD and may also hold promise as a predictor of frailty. Research has demonstrated that AAC correlates with reduced grip strength (Ramírez-Vélez et al., 2021), compromised cognitive abilities (Wei et al., 2021), heightened risk of dementia in later stages of life (Porter et al., 2022), and accelerated weight loss (Smith et al., 2024) among middle-aged and older populations. These factors have already been recognized as significant contributors to frailty risk. The relationship between AAC and frailty has been underexplored, with current research primarily centered around specific diseases. Preliminary findings from a small sample of older individuals have shown that the robust group exhibited lower levels of vascular calcification on vertebral imaging compared to the frailty group. Additionally, femoral vascular calcification was inversely correlated with both bone mineral density and muscle mass (Idoate et al., 2017). Subsequently, Lee SY's study was the first to identify a direct positive correlation between the severity of AAC and frailty among older adults (Lee et al., 2020). Our findings significantly expand current understanding by generalizing the results to middle-aged populations and utilizing a sample representative of the United States. Moreover, we employed a more precise and widely accepted method for defining frailty, namely the frailty index, incorporating up to 49 items for calculation.

The potential mechanisms underlying the association between AAC and frailty can be elucidated through the following speculation. Inflammation should be regarded as a crucial link connecting AAC to frailty, with the cumulative manifestations of inflammation contributing to the development of frailty (Ferrucci and Fabbri, 2018). Aging is intricately linked to immune dysregulation, primarily marked by elevated levels of circulating pro-inflammatory markers (Li and Ma, 2024). Prolonged and persistent inflammation can detrimentally impact health, increasing susceptibility to prevalent diseases such as CVD, cancer, dementia, and depression (Fabbri et al., 2015). Consequently, this cascade of events ultimately contributes to the onset of frailty. Meanwhile, vascular calcification is linked to intimal calcification, a process characterized by lipid deposition that elicits a potent inflammatory response. Importantly, the risk factors predisposing individuals to CVD also promote this form of calcification (Vieceli Dalla Sega et al., 2022). Vascular calcification can result in vascular stiffness and reduced aortic compliance, leading to elevated blood pressure (Pan et al., 2020). Hypertension, in turn, is associated with a range of diseases. Furthermore, vascular calcification disrupts blood flow to vital organs. Long-term cerebral ischemia and hypoxia represent crucial mechanisms underlying dementia (Porter et al., 2022). Additionally, calcification of mesenteric vessels can impede nutrient absorption, contributing to rapid weight loss (Smith et al., 2024). It is noteworthy that a study has highlighted AAC as an indicator of the interconnection between atherosclerosis and skeletal fragility, and AAC correlates with alterations in bone strength (Mazziotti et al., 2020).

Frailty is closely associated with cancer recurrence and postoperative complications (Imaoka et al., 2024a). This study confirms the correlation between AAC and frailty. Patients with high AAC are often accompanied by risk factors such as advanced age, obesity, and diabetes, which negatively impact gastrointestinal surgeries and postoperative outcomes (Imaoka et al., 2024a). Moreover, AAC is directly associated with the risk of postoperative complications and tolerance to adjuvant chemotherapy (Imaoka et al., 2024b). Therefore, AAC serves as a valuable clinical marker for assessing frailty and postoperative risks, providing important guidance for individualized treatment strategies. AAC and frailty are both independently associated with an increased risk of falls and fractures, particularly in older adults (Dalla Via et al., 2023). AAC reflects systemic vascular calcification and stiffness, which may impair physical function and balance, thereby contributing to a higher likelihood of falls (Gebre et al., 2021). Frailty, characterized by reduced physiological reserves and increased vulnerability to external stressors, further exacerbates this risk. The combination of AAC and frailty may have a synergistic effect, amplifying the probability of adverse outcomes such as fractures, which can lead to significant morbidity, mortality, and healthcare burden. From a public health perspective, early identification and management of individuals with AAC and frailty are critical for implementing preventive strategies, reducing fall-related injuries, and improving overall health outcomes in aging populations (Gebre et al., 2023).

Our study possesses several significant strengths. Firstly, our findings stem from a substantial national random sample, ensuring their broad applicability to the adult noninstitutionalized population of the United States. Secondly, we derived AAC data from objective clinical sources. Simultaneously, we utilized the Frailty Index, a state-of-the-art quantitative instrument, to precisely define frailty. Additionally, our study

meticulously accounted for numerous recognized potential confounders, bolstering the robustness and credibility of our findings. This study also has several limitations. Firstly, due to its cross-sectional design, we cannot infer a causal relationship between AAC and frailty. Secondly, some data on frailty status were collected through questionnaires, which may introduce recall bias. Furthermore, frailty is a dynamic process that increases with aging, and longitudinal modeling algorithms have been developed in previous study to capture the temporal evolution of frailty (Li et al., 2023). However, such algorithms could not be applied in the NHANES database. Lastly, our sample was derived from a national survey conducted in the United States, necessitating further clarification regarding the generalizability of our findings.

5. Conclusion

Among middle-aged and older adults in the United States, a positive association exists between AAC and frailty. Our findings suggest that the AAC score holds promise as a valuable tool for the early identification of frailty. Further high-quality studies are warranted to validate our findings and establish a causal relationship between the two variables.

Funding

This study was supported by the Key Research and Development Task Special in Xinjiang Uygur Autonomous Region (Grant No. 2022B03022–3) and national natural science foundation of China (Grant No. 82360090).

Consent for publication

No applicable.

Ethics approval and consent to participate

The study protocols of NHANES were approved by the NCHS Research Ethics Review Board and participant written informed consent was obtained (https://www.cdc.gov/nchs/nhanes). The additional ethical review was no longer required for the present study due to the usage of publicly available data without identifiable personal information.

CRediT authorship contribution statement

Rena Rehemuding: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kaisaierjiang Kadier:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xinliang Peng:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pengfei Liu:** Visualization, Software. **Diliyaer Dilixiati:** Visualization, Software. **Aikeliyaer Ainiwaer:** Formal analysis, Data curation. **Xiaozhu Liu:** Formal analysis, Data curation. **Xiangtao Liu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration. **Xiang Ma:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Xiang Ma reports financial support was provided by the Key Research and Development Task Special in Xinjiang Uygur Autonomous Region (Grant No. 2022B03022–3) and national natural science foundation of China (Grant No. 82360090). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank all members of the NHANES teams for surveys and data collection throughout the United States.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2025.102994.

Data availability

This study is a secondary analysis based on a publicly available database and the raw data can be found on the website: https://www.cdc.gov/nchs/nhanes/index.htm.

References

Blodgett, J., Theou, O., Kirkland, S., Andreou, P., Rockwood, K., 2015. Frailty in NHANES: comparing the frailty index and phenotype. Arch. Gerontol. Geriatr. 60, 464–470. https://doi.org/10.1016/j.archger.2015.01.016.

Criqui, M.H., Denenberg, J.O., McClelland, R.L., Allison, M.A., Ix, J.H., Guerci, A., et al., 2014. Abdominal aortic calcium, coronary artery calcium, and cardiovascular morbidity and mortality in the multi-ethnic study of atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 34, 1574–1579. https://doi.org/10.1161/ATVBAHA.114.303268.

Dalla Via, J., Gebre, A.K., Smith, C., Gilani, Z., Suter, D., Sharif, N., et al., 2023. Machine-learning assessed abdominal aortic calcification is associated with long-term fall and fracture risk in community-dwelling older Australian women. J. Bone Miner. Res. 38, 1867–1876. https://doi.org/10.1002/jbmr.4921.

Damluji, A.A., Chung, S.-E., Xue, Q.-L., Hasan, R.K., Moscucci, M., Forman, D.E., et al., 2021. Frailty and cardiovascular outcomes in the National Health and aging trends study. Eur. Heart J. 42, 3856–3865. https://doi.org/10.1093/eurheartj/ehab468.

Dent, E., Martin, F.C., Bergman, H., Woo, J., Romero-Ortuno, R., Walston, J.D., 2019. Management of frailty: opportunities, challenges, and future directions. Lancet 394, 1376–1386. https://doi.org/10.1016/S0140-6736(19)31785-4.

Dent, E., Dalla Via, J., Bozanich, T., Hoogendijk, E.O., Gebre, A.K., Smith, C., et al., 2024. Frailty increases the long-term risk for fall and fracture-related hospitalizations and all-cause mortality in community-dwelling older women. J. Bone Miner. Res. 39, 222–230. https://doi.org/10.1093/jbmr/zjad019.

Fabbri, E., An, Y., Zoli, M., Simonsick, E.M., Guralnik, J.M., Bandinelli, S., et al., 2015. Aging and the burden of multimorbidity: associations with inflammatory and anabolic hormonal biomarkers. J. Gerontol. A Biol. Sci. Med. Sci. 70, 63–70. https://doi.org/10.1093/gerona/glu127.

Fan, J., Yu, C., Guo, Y., Bian, Z., Sun, Z., Yang, L., et al., 2020. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. Lancet Public Health 5, e650–e660. https://doi.org/10.1016/S2468-2667(20)30113-4.

Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15, 505–522. https://doi.org/10.1038/s41569-018-0064-2.

Gebre, A.K., Sim, M., Rodríguez, A.J., Hodgson, J.M., Blekkenhorst, L.C., Szulc, P., et al., 2021. Abdominal aortic calcification is associated with a higher risk of injurious fall-related hospitalizations in older Australian women. Atherosclerosis 328, 153–159.

Gebre, A.K., Lewis, J.R., Leow, K., Szulc, P., Scott, D., Ebeling, P.R., et al., 2023. Abdominal aortic calcification, bone mineral density, and fractures: a systematic review and Meta-analysis of observational studies. J. Gerontol. A Biol. Sci. Med. Sci. 78, 1147–1154.

Górriz, J.L., Molina, P., Cerverón, M.J., Vila, R., Bover, J., Nieto, J., et al., 2015. Vascular calcification in patients with nondialysis CKD over 3 years. Clin. J. Am. Soc. Nephrol. 10, 654–666. https://doi.org/10.2215/CJN.07450714.

Hakeem, F.F., Bernabé, E., Sabbah, W., 2021. Association between Oral health and frailty among American older adults. J. Am. Med. Dir. Assoc. 22, 559–563.e2. https://doi.org/10.1016/j.jamda.2020.07.023.

Hanlon, P., Nicholl, B.I., Jani, B.D., Lee, D., McQueenie, R., Mair, F.S., 2018. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK biobank participants. Lancet Public Health 3, e323–e332. https://doi.org/10.1016/S2468-2667(18)30091-4.

He, D., Wang, Z., Li, J., Yu, K., He, Y., He, X., et al., 2024. Changes in frailty and incident cardiovascular disease in three prospective cohorts. Eur. Heart J. 45, 1058–1068. https://doi.org/10.1093/eurheartj/ehad885.

Hoogendijk, E.O., Afilalo, J., Ensrud, K.E., Kowal, P., Onder, G., Fried, L.P., 2019. Frailty: implications for clinical practice and public health. Lancet 394, 1365–1375. https://doi.org/10.1016/S0140-6736(19)31786-6.

Idoate, F., Cadore, E.L., Casas-Herrero, A., Zambom-Ferraresi, F., Martínez-Velilla, N., Rodriguez-Mañas, L., et al., 2017. Noncoronary vascular calcification, bone mineral

density, and muscle mass in institutionalized frail nonagenarians. Rejuvenation Res. 20, 298–308. https://doi.org/10.1089/rej.2016.1868.
Imaoka, Y., Ohira, M., Akabane, M., Sasaki, K., Ohdan, H., 2024a. Abdominal aortic calcification among gastroenterological and transplant surgery. Ann Gastroenterol Surg 8, 987–998. https://doi.org/10.1002/ags3.12816.
Imaoka, K., Shimomura, M., Okuda, H., Yano, T., Akabane, S., Ohira, M., et al., 2024b. Abdominal aortic calcification as a predictor of incomplete adjuvant chemotherapy in stage III colorectal Cancer: a retrospective cohort study. Cureus 16, e71288. https://doi.org/10.7759/cureus.71288.
Jiang, Z., Wang, J., Cai, X., Wang, P., Liu, S., 2023. L-shaped association of serum α-klotho and frailty among the middle-aged and older adults: results from NHANES 2007-2016. BMC Geriatr. 23, 716. https://doi.org/10.1186/s12877-023-04324-z.
Johnson, C.L., Dohrmann, S.M., Burt, V.L., Mohadjer, L.K., 2014. National health and nutrition examination survey: sample design, 2011-2014. Vital Health Stat. 2, 1–33.
Kadier, K., Abulizi, A., Ainiwaer, A., Rehemuding, R., Ma, X., Ma, Y.-T., 2023. Unravelling the link between periodontitis and abdominal aortic calcification in the US adult population: a cross-sectional study based on the NHANES 2013-2014. BMJ Open 13, e068931. https://doi.org/10.1136/bmjopen-2022-068931.
Kauppila, L.I., Polak, J.F., Cupples, L.A., Hannan, M.T., Kiel, D.P., Wilson, P.W., 1997. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis 132, 245–250. https://doi.org/10.1016/s0021-9150(97)00106-8.
Lee, S.-Y., Chao, C.-T., Huang, J.-W., Huang, K.-C., 2020. Vascular calcification as an Underrecognized risk factor for frailty in 1783 community-dwelling elderly individuals. J. Am. Heart Assoc. 9, e017308. https://doi.org/10.1161/JAHA.120.017308.
Li, X., Ma, L., 2024. From biological aging to functional decline: insights into chronic inflammation and intrinsic capacity. Ageing Res. Rev. 93, 102175. https://doi.org/10.1016/j.arr.2023.102175.
Li, C., Ma, Y., Hua, R., Zheng, F., Xie, W., 2023. Utility of SCORE2 risk algorithm for predicting life course accelerated frailty and physical function decline. J. Cachexia. Sarcopenia Muscle 14, 596–605. https://doi.org/10.1002/jcsm.13165.
Mazziotti, G., Tupputi, U., Ferrante, G., Guglielmi, G., 2020. Abdominal aortic calcification as a marker of relationship between atherosclerosis and skeletal fragility. J. Clin. Densitom. 23, 539–542. https://doi.org/10.1016/j.jocd.2020.05.001.
Mitnitski, A.B., Mogilner, A.J., Rockwood, K., 2001. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 1, 323–336. https://doi.org/10.1100/tsw.2001.58.
Pan, W., Jie, W., Huang, H., 2020. Vascular calcification: molecular mechanisms and therapeutic interventions. MedComm 2023 (4), e200. https://doi.org/10.1002/mco2.200.
Porter, T., Sim, M., Prince, R.L., Schousboe, J.T., Bondonno, C., Lim, W.H., et al., 2022. Abdominal aortic calcification on lateral spine images captured during bone density testing and late-life dementia risk in older women: a prospective cohort study. Lancet Reg Health West Pac 26, 100502. https://doi.org/10.1016/j.lanwpc.2022.100502.
Ramírez-Vélez, R., García-Hermoso, A., Correa-Rodríguez, M., Lobelo, F., González-Ruiz, K., Izquierdo, M., 2021. Abdominal aortic calcification is associated with decline in handgrip strength in the U.S. adult population ≥40 years of age. Nutr. Metab. Cardiovasc. Dis. 31, 1035–1043. https://doi.org/10.1016/j.numecd.2020.11.003.
Schousboe, J.T., Lewis, J.R., Kiel, D.P., 2017. Abdominal aortic calcification on dual-energy X-ray absorptiometry: methods of assessment and clinical significance. Bone 104, 91–100. https://doi.org/10.1016/j.bone.2017.01.025.
Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8, 24. https://doi.org/10.1186/1471-2318-8-24.
Shrauner, W., Lord, E.M., Nguyen, X.-M.T., Song, R.J., Galloway, A., Gagnon, D.R., et al., 2022. Frailty and cardiovascular mortality in more than 3 million US veterans. Eur. Heart J. 43, 818–826. https://doi.org/10.1093/eurheartj/ehab850.
Si, H., Jin, Y., Qiao, X., Tian, X., Liu, X., Wang, C., 2021. Predictive performance of 7 frailty instruments for short-term disability, falls and hospitalization among Chinese community-dwelling older adults: a prospective cohort study. Int. J. Nurs. Stud. 117, 103875. https://doi.org/10.1016/j.ijnurstu.2021.103875.
Smith, C., Sim, M., Dalla Via, J., Gebre, A.K., Zhu, K., Lim, W.H., et al., 2024. Extent of abdominal aortic calcification is associated with incident rapid weight loss over 5 years: the Perth longitudinal study of ageing women. Arterioscler. Thromb. Vasc. Biol. 44, e54–e64. https://doi.org/10.1161/ATVBAHA.123.320118.
Stekhoven, D.J., Bühlmann, P., 2012. MissForest–non-parametric missing value imputation for mixed-type data. Bioinformatics 28, 112–118. https://doi.org/10.1093/bioinformatics/btr597.
Vieceli Dalla Sega, F., Fortini, F., Severi, P., Rizzo, P., Gardi, I., Cimaglia, P., et al., 2022. Cardiac calcifications: phenotypes, mechanisms, clinical and prognostic implications. Biology (Basel) 11, 414. https://doi.org/10.3390/biology11030414.
von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., et al., 2007. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370, 1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X.
Wei, J., Ali, M.K., Wang, T., Xu, H., 2021. Abdominal aortic calcification and cognitive function among older adults: cross-sectional analysis of National Health and nutrition examination survey, 2013-2014. Int. J. Geriatr. Psychiatry 36, 1778–1784. https://doi.org/10.1002/gps.5599.
Wilson, P.W., Kauppila, L.I., O'Donnell, C.J., Kiel, D.P., Hannan, M., Polak, J.M., et al., 2001. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. Circulation 103, 1529–1534. https://doi.org/10.1161/01.cir.103.11.1529.
Yang, S.-W., Yang, H.-F., Chen, Y.-Y., Chen, W.-L., 2021. Unraveling the link between metabolic syndrome and abdominal aortic calcification. Nutr. Metab. Cardiovasc. Dis. 31, 464–471. https://doi.org/10.1016/j.numecd.2020.10.003.