

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

# **BMJ Open**

## Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-086075
Article Type:	Original research
Date Submitted by the Author:	05-Mar-2024
Complete List of Authors:	Won, Ki-Bum; Chung-Ang University Choi, Su-Yeon ; Seoul National University Hospital, Internal Medicine Chun, Eun Ju; Seoul National University Bundang Hospital Park, Sung Hak; Gangnam Heartscan Clinic Sung, Jidong; Samsung Medical Center Jung, Hae Ok; The Catholic University of Korea Chang, Hyuk Jae; Yonsei University Health System
Keywords:	Cardiac Epidemiology < CARDIOLOGY, PUBLIC HEALTH, Cardiovascular imaging < RADIOLOGY & IMAGING, PREVENTIVE MEDICINE





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies



2							
3 4							
5	1	Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification					
6 7	2	progression in an asymptomatic population of Korean adults: An observational cohort study					
8 9	3						
10 11 12	4	Running title: Serum albumin and CAC progression					
12 13 14	5						
15 16	6	Ki-Bum Won <sup>1</sup> , Su-Yeon Choi <sup>2</sup> , Eun Ju Chun <sup>3</sup> , Sung Hak Park <sup>4</sup> , Jidong Sung <sup>5</sup> , Hae Ok Jung <sup>6</sup> , Hyuk-Jae					
17 18	7	Chang <sup>7</sup> *					
19 20	8						
21 22	9	Affiliations:					
23 24	10	<sup>1</sup> Division of Cardiology, Chung-Ang University Gwangmyeong Medical Center, Chung-Ang					
25 26	11	University College of Medicine, Gwangmyeong, South Korea					
27 28	12	<sup>2</sup> Division of Cardiology, Healthcare System Gangnam Center, Seoul National University Hospital,					
29 30 31	13	3 Seoul, South Korea					
32 33	14	<sup>3</sup> Division of Radiology, Seoul National University Bundang Hospital, Seongnam, South Korea					
34 35	15	<sup>4</sup> Division of Radiology, Gangnam Heartscan Clinic, Seoul, South Korea					
36 37	16	<sup>5</sup> Division of Cardiology, Heart Stroke & Vascular Institute, Samsung Medical Center, Seoul, South					
38 39	17	Korea					
40 41	18	<sup>6</sup> Division of Cardiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of					
42 43	19	Korea, Seoul, South Korea					
44 45	20	<sup>7</sup> Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University Health System, Seoul, South					
46 47	21	Korea					
48 49	22						
50 51 52	23	Word count: 3319					
52 53 54	24						
54 55 56	25	Correspondence:					
57 58	26	Hyuk-Jae Chang, MD, PhD 1					
59 60							

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Division of Cardiology, Severance Cardiovascular Hospital,

50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea

Tel.: +82(0)2 22288460; Fax: +82(0)2 3932041

Yonsei University College of Medicine,

Yonsei University Health System

E-mail: hjchang@yuhs.ac

Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center,

3	
4	27
5	27
6 7 8	28
8	29
9 10	
11 12	30
13	31
14 15	32
16	
17 18	33
19	
20	
21 22 23 24 25	
23	
24	
25 26	
20 27	
28	
29	
30 31	
32	
33	
34 35	
36	
37	
38	
39 40	
41	
42	
43 44	
44 45	
46	
47	
48 49	
50	
51	
52 53	
53 54	
55	
56	
57 58	
58 59	

60

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

#### ABSTRACT

**OBJECTIVES** This study evaluated the association between serum albumin levels and coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminemia at baseline. **DESIGN** Observational cohort study SETTING Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single ethnicity, multicenter, and observational registry were analyzed **PARTICIPANTS** A total of 12344 Korean adults with baseline albumin level of >3.5 g/dL ( $51.7 \pm 8.5$ years; 84.3% male) were included. The median interscan period was 3.0 (2.0-4.8) years. All participants were stratified into three groups based on serum albumin tertile. MAIN OUTCOMES MEASURES Association of serum albumin with the risk of CAC progression adjusted for relevant covariates was analyzed using logistic regression models. CAC progression was defined as a square root ( $\sqrt{}$ ) transformed difference between the baseline and follow-up coronary artery calcium score (CACS) ( $\Delta \sqrt{\text{transformed CACS}}$ ) of  $\geq 2.5$ . Annualized  $\Delta \sqrt{\text{transformed CACS}}$  was defined as  $\Delta \sqrt{\text{transformed CACS divided by inter-scan period.}}$ **RESULTS** With increasing serum albumin tertiles, the annualized  $\Delta \sqrt{\text{transformed CACS}}$  (I [lowest]: 0.16 (0-1.24) vs. II: 0 (0-1.09) vs. III [highest]: 0 (0-1.01) and the incidence of CAC progression (I: 36.6% vs. II: 31.3% vs. III: 25.0%) were decreased despite higher prevalence of hypertension, diabetes, and hyperlipidemia (all P <0.05). Serum albumin levels were inversely related to the annualized  $\Delta \sqrt{\text{transformed CACS}}$  and the risk of CAC progression among overall participants. This inverse association between serum albumin levels and the risk of CAC progression was consistently observed in baseline condition with CACS of 1–100 after adjusting for confounding factors. **CONCLUSIONS** Serum albumin levels are inversely associated with CAC progression, especially in conditions with non-heavy CAC at baseline. Key Words: albumin; atherosclerosis; coronary artery calcium score

2 3		
4 5	60	
6 7	61	STRENGTHS AND LIMITATIONS OF THIS STUDY
8 9	62	
10 11	63	• Longitudinal study with large sample size analyzing the data of multicenter and observational
12 13	64	cohort registry
14 15	65	• Assessment of the association of serum albumin levels with coronary artery calcification (CAC)
16 17 18	66	progression focusing on the baseline coronary artery calcium score
19 20	67	• Adjustment of traditional risk factors to evaluate independent relationship between serum albumin
21 22	68	levels and the risk of CAC progression
23 24	69	• Difficulty in generalizing the results of current study because of the single-ethnicity participants
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59		<form><text></text></form>

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

### 

70 INTRODUCTION

Atherosclerotic coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide.<sup>1</sup> In asymptomatic populations, the coronary artery calcium score (CACS) has been used to stratify cardiovascular (CV) risk based on the evidence that the CACS provides strong prognostic information across age, sex, and ethnicity.<sup>2–4</sup> Moreover, the progression of coronary artery calcification (CAC) has additive prognostic values beyond traditional risk factors, particularly in the absence of heavy baseline CAC.<sup>5,6</sup> Thus, CACS determined using computed tomography (CT) has a substantial role in assessing CV risk for primary prevention.<sup>7,8</sup>

Albumin is a major protein accounting for more than half of the total serum composition. Previous studies have revealed that serum albumin has several physiological properties, including anti-oxidant, anti-inflammatory, and anti-platelet aggregation activities.<sup>9–13</sup> The normal range of serum albumin levels is defined to be within 3.5-5.5 g/dL in clinical practice. Recent evidence has suggested that low serum albumin levels are strongly associated with the increased risk of CHD and mortality beyond traditional risk factors.<sup>14–17</sup> However, data regarding the association between serum albumin levels and coronary atherosclerotic changes in asymptomatic adults are lacking. In addition, although previous studies have revealed that 1) the absence of CAC confers a low CV event risk<sup>2,18</sup> and 2) clinical risk factors are less predictive for the progression of coronary atherosclerosis compared to the baseline coronary plaque burden,<sup>19</sup> little is known regarding the association of serum albumin levels with the risk of CAC progression according to baseline CAC status. Therefore, the present study aimed to evaluate the association between serum albumin levels and the risk of CAC progression in an asymptomatic population of Korean adults without hypoalbuminemia at baseline. 

## 92 METHODS

## 93 Study population and design

This study analyzed the data of Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single-ethnicity, multicenter, and observational registry with a self-referral setting for

#### **BMJ** Open

asymptomatic subjects who underwent general health checkups at six healthcare centers in South Korea (Severance Cardiovascular Hospital; Samsung Medical Center; Seoul St. Mary's Hospital; Seoul National University Hospital; Seoul National University Bundang Hospital; Gangnam Heartscan Clinic). A total of 93,707 patients were enrolled in the registry between December 2012 and August 2016. Among these participants, 12353 who underwent at least two CAC scans with available serum albumin level data were identified. After excluding nine patients with hypoalbuminemia (serum albumin level <3.5 g/dL), 12344 were included in the present study. All data were obtained during visits to each healthcare center. Self-reported medical questionnaires were used to obtain information on medical histories. Information on the medical histories of hypertension, diabetes, hyperlipidemia, current smoking, and alcohol consumption status of each participant was systematically collected. Height, weight, and blood pressure were measured during healthcare center visits. Blood pressure was measured using an automatic manometer on the right arm after resting for at least 5 mins. Body mass index (BMI) was calculated as weight (kg)/height (m<sup>2</sup>). All blood samples, including those for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, hemoglobin A1C (HbA1C), albumin, and creatinine were obtained after at least 8 h of fasting and analyzed. Hypertension was defined as systolic blood pressure (SBP)  $\geq 140$ mmHg or diastolic blood pressure (DBP) ≥90 mmHg, previous diagnosis of hypertension, or antihypertensive medication. Diabetes was defined as a fasting glucose level of  $\geq$ 126 mg/dL, HbA1C level of  $\geq 6.5\%$ , a referral diagnosis of diabetes, or receiving anti-diabetic treatment. Hyperlipidemia was defined as a total cholesterol level of  $\geq$ 240 mg/dL, a referral diagnosis of hyperlipidemia, or receiving anti-hyperlipidemic treatment. Obesity was defined as a BMI of  $\geq 25.0 \text{ kg/m}^2$  following the Korean Society for the Study of Obesity Guidelines. Participants were categorized into three groups based on their serum albumin tertiles.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

In this study, CACS was measured based on the scoring system previously described by Agatston
 et al.<sup>20</sup> The baseline CACS was divided into four groups: CACS of 0, 1–10, 11–100, and >100,
 respectively. The progression of CAC was defined as a difference ≥2.5 between the square roots (√) of

the baseline and follow-up CACS ( $\Delta\sqrt{\text{transformed CACS}}$ ),<sup>5,21</sup> considering interscan variability and the proportion of baseline CACS of 0 (56.2%). Annualized  $\Delta \sqrt{\text{transformed CAC}}$  was defined as  $\Delta\sqrt{\text{transformed CAC divided by interscan period. All computed tomography (CT) scans to assess CAC}$ were obtained using >16-slice multidetector CT scanners (Siemens 16-slice Sensation [Siemens AG, Munich, Germany], Philips Brilliance 256 iCT [Philips Healthcare, Amsterdam, The Netherlands], Philips Brilliance 40 channel MDCT [Philips Healthcare], and GE 64-slice Lightspeed [GE Healthcare] Chicago, IL, USA]). Informed consent was obtained from all participants at each of centers. All methods were performed following relevant guidelines and regulations. The appropriate institutional review board of Severance Cardiovascular Hospital approved the study protocol (IRB No: 4-2014-0309).

**Statistical analysis** 

Continuous variables are expressed as the mean  $\pm$  standard deviation or the median (interquartile range), and categorical variables are presented as absolute values and percentages. After checking the distribution status of independent variables, the one-way analysis of variance test or the Kruskal-Wallis test was used for continuous variables, and the  $\chi^2$  test or Fisher's exact test was used for categorical variables, as appropriate. Univariable regression analyses were performed to evaluate the relation of clinical variables with 1) annualized  $\Delta \sqrt{\text{transformed CACS}}$  and 2) the risk of CAC progression. Subsequently, multiple logistic regression models were used to assess the association of serum albumin levels with the risk of CAC progression considering the baseline categorical CACS (Model 1, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, and alcohol consumption; Model 2, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine levels, baseline CACS, and interscan period). The forced entry method was used to enter the independent variables into the multiple regression models. All statistical analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at p < 0.05 in all analyses.

## 148 Patient and public involvement

**Baseline characteristics** 

RESULTS

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plansof our research.

**Table 1** presents the baseline characteristics of the participants. The mean age of the participants155was  $51.7 \pm 8.5$  years, and 10,400 (84.3%) were men. The mean age decreased with increasing serum156albumin tertiles. In contrast, the mean SBP, DBP, total cholesterol, triglyceride, LDL-C, fasting glucose,157and HbA1C levels increased with increasing serum albumin levels. Similarly, the proportion of male158sex and the prevalence of hypertension, diabetes, hyperlipidemia, and alcohol consumption increased159with increasing serum albumin tertiles. Significant differences were not observed in the HDL-C and160creatinine levels or in the prevalence of obesity and current smoking across the serum albumin tertiles.

## 162 Baseline and changes of CAC according to the serum albumin tertiles

The median interscan period was 3.0 (2.0–4.8) years. During follow-up, the mean changes of  $\sqrt{\text{transformed CACS}}$  and annualized  $\sqrt{\text{transformed CACS}}$  were decreased with increasing serum albumin tertiles. The incidence of the CAC progression in overall participants was 30.6%; it significantly decreased with increasing serum albumin tertiles. The incidence of CAC progression at baseline CACS of 0, 1–10, 11–100, and >100 was 13.0%, 57.6%, 50.4%, and 52.6%, respectively; the progression of CAC was less observed with increasing serum albumin tertiles in all baseline CACS groups (**Table 2**).

## 171 Association between clinical variables and CAC changes

Univariable linear regression analysis showed that age, male sex, hypertension, diabetes,
hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine, and baseline CACS

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

were positively related to the annualized  $\Delta \sqrt{\text{transformed CACS}}$ ; in contrast, serum albumin levels were inversely related to the annualized  $\Delta \sqrt{\text{transformed CACS}}$ . In univariable logistic regression analysis, age, male sex, hypertension, diabetes, hyperlipidemia, obesity, alcohol consumption, serum creatinine level, and baseline CACS were associated with an increased risk of progression of CAC. However, elevated serum albumin levels were associated with a decreased risk of progression of CAC (**Table 3**). The results of the subgroup analysis of the estimated risk of serum albumin levels for CAC progression are presented in **Figure 1**.

182 Serum albumin levels and CAC progression according to baseline CACS

In multiple logistic regression models, serum albumin levels were significantly associated with the decreased risk of CAC progression in overall participants. Multiple linear regression models regarding the association between serum albumin levels and the annualized  $\Delta \sqrt{\text{transformed CACS}}$  with consecutive adjustment of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS showed the consistent results (Supplementary table 1). According to the categorical CACS at baseline, model 1 showed that serum albumin levels were consistently associated with the risk of CAC progression in participants with baseline CACS of 1–10, 11–100, and >100 except that of 0. In the model 2, the significant association between serum albumin levels and the risk of CAC progression was observed in participants with baseline CACS of 1–10 and 11–100 (Table 4).

**DISCUSSION** 

The present study observed that the incidence of CAC progression significantly decreased with increasing serum albumin levels despite a positive relation between serum albumin levels and the prevalence of hypertension, diabetes, and hyperlipidemia in asymptomatic adults without hypoalbuminemia at baseline. An inverse association between serum albumin levels and the risk of progression of CAC was consistently observed after adjusting for confounding factors. Notably, no 

significant association between serum albumin levels and the risk of progression of CAC was identified
in participants with CACS of 0 as well as in those with CACS of >100 at baseline. These results suggest
that high serum albumin levels have a protective effect for the progression of CAC in asymptomatic
adults, particularly in those with non-heavy CAC at baseline.

Several studies have reported a positive association between serum albumin levels and metabolic risk factors, such as blood pressure, insulin resistance, and lipid profile.<sup>22–26</sup> A recent cohort study from the Kuopio Ischaemic Heart Disease population found a linear and positive association between serum albumin levels and type 2 diabetes but not improving diabetes risk prediction during a mean follow-up of 20.4 years.<sup>27</sup> Similar to the previous data reported by Danesh et al. in their cross-sectional investigation of individuals with no history of CHD,<sup>25</sup> we observed that serum albumin levels were positively associated with SBP, DBP, and triglyceride and LDL-C levels among our participants without hypoalbuminemia at baseline (Supplementary Table 2). Although the mechanistic pathways for this association between serum albumin and metabolic disorders are unclear, a higher intake of dietary protein reportedly contributes to the positive association between serum albumin levels and metabolic syndrome.<sup>28</sup> Interestingly, despite a positive relation of serum albumin levels with metabolic abnormalities, numerous studies have shown that serum albumin levels are inversely related to the prognosis with a cardioprotective effect.<sup>14–17</sup>

It is well-known that serum albumin has an essential blood anti-oxidant property as well as physiological activities including anti-inflammation and anti-platelet aggregation.<sup>9-13, 29</sup> Based on these findings, several studies have evaluated the relation between serum albumin levels and subclinical atherosclerosis. The National Heart, Lung, and Blood Institute Family Heart Study reported that lower serum albumin levels were not associated with an increased risk of prevalent carotid atherosclerosis in men or women among 2,072 participants.<sup>30</sup> However, Ishizaka et al. demonstrated somewhat different results that higher serum albumin levels were inversely associated with the prevalence of early carotid atherosclerosis, although they were positively associated with the prevalence of metabolic syndrome in 8142 Japanese individuals.<sup>26</sup> To our knowledge, there are no studies with a large sample size on the 

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

effect of serum albumin levels on coronary atherosclerotic changes, particularly in conditions without hypoalbuminemia. In this study, we observed an independent and inverse association between serum albumin levels and the progression of CAC in 12,344 asymptomatic participants with normal range of serum albumin levels beyond traditional risk factors, particularly in those with non-heavy CAC. This finding suggests that serum albumin has anti-atherogenic effects, irrespective of its positive association with metabolic abnormalities. However, the superior utility of high serum albumin levels for improving CV risk prediction over and above traditional risk factors is questionable. Also, the present study could not evaluate the association of serum albumin levels with non-calcified plagues or vulnerable plagues in coronary arteries because this data is based on the evaluation of CACS performed in asymptomatic adult population. Further large-scale prospective investigations are required to confirm these issues.

The Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter substudy with a mean follow-up of  $5.9 \pm 1.2$  years recently identified that further prognostic benefit was not offered by coronary CT angiography findings over CACS and traditional risk factors in 1,226 asymptomatic adults.<sup>31</sup> Blaha et al.<sup>18</sup> reported that the absence of CAC predicted survival, with 10-year event rates of approximately 1% in 44,052 consecutive asymptomatic patients referred for CAC testing during a mean follow-up of  $5.6 \pm 2.6$  years. Similarly, the Multi-Ethnic Study of Atherosclerosis study found consistent results among 6,722 participants during a median follow-up of 3.8 years, irrespective of racial and ethnic differences.<sup>2</sup> In this study, despite the independent and inverse association between serum albumin levels and the progression of CAC in overall participants, this phenomenon was not observed in participants without CAC or those with heavy CAC at baseline. These results indicate that 1) the absence of CAC reflects a low CV risk status, which is less affected by serum albumin levels in asymptomatic populations and 2) it is hard to predict the progression of CAC using specific biomarkers in condition with heavy CAC at baseline as previous studies have suggested. 32,33

This study had some limitations. First, this study was performed in a healthy population who
voluntarily participated in the health check-ups, which may have resulted in a selection bias. Second,
this was a retrospective study, which may have been influenced by unidentified confounders. Third,

#### **BMJ** Open

data on the participants' physical activity were unavailable. Fourth, we could not control for the effects of medications for hypertension, diabetes, and hyperlipidemia on the progression of CAC because of the observational design. Fifth, a sample size of baseline CACS >100 was relatively small compared to that of other baseline categorical CACS. Finally, this study included only a Korean population, which may limit generalization. Nevertheless, this study is unique in that we evaluated the association between serum albumin levels and the risk of CAC progression after considering baseline CAC status in an asymptomatic Asian population with normal serum albumin levels.

260 CONCLUSIONS

The current study observes that serum albumin levels have an independent and inverse association with the progression of CAC despite their positive relation with metabolic abnormalities in asymptomatic adults without hypoalbuminemia, particularly in those with non-heavy CAC at baseline. Considering the interaction between clinical variables and serum albumin levels regarding the risk of CAC progression in subgroup analysis, further prospective investigations to evaluate the significance of serum albumin levels for subclinical coronary atherosclerosis focusing on diabetes and hyperlipidemia should be necessary.

- 3 268
- <sup>)</sup> 269 **Contributiors**

Study hypothesis and design: KBW and HJC. Data acquisitions: KBW, SYC, EJC, SHP, JS, HOJ, and
HJC. Statistical analyses: KBW and HJC. Writing of the initial versions of the manuscript: KBW.
Responsible for the overall content as the guarantor: HJC. All authors read, reviewed and provided
feedback for the final manuscript.

 275 Funding

276 This research was supported by the Korean Medical Device Development Fund grant funded by the

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

2	
3 4	277
5 6	278
7 8	279
9 10	
11 12	280
13 14	281
15 16	282
10 17 18	283
19 20	284
21 22	285
23 24	286
25 26 27	287
27 28	288
29 30	289
31 32 33	290
34 35	291
36 37	292
38 39	293
40 41	294
42 43	295
44 45	296
46 47	297
48 49	298
50 51	299
52 53	300
54 55	
56 57	301
58	
59 60	

1

77	Korean government (Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the
78	Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (Project Number: 1711139017)
79	and the Chung-Ang University Research Grants in 2024.
80	
81	Competing interests
82	The authors declare no competing interests.
83	
84	Patient and public involvement
85	Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
86	plans of this research.
87	
88	Patient consent for publication
89	Not applicable.
90	
91	Ethics approval
92	This study involves human participants and was approved by the appropriate institutional review board
93	of Severance Cardiovascular Hospital (IRB No: 4-2014-0309). Participant consent is not required for
94	the KOICA studies using purely observational data.
95	
96	Data availability statement
97	The datasets used and analyzed in the current study are available from the corresponding author upon
98	reasonable request.
99	
00	ORCID iDs
01	Hyuk-Jae Chang https://orcid.org/0000-0002-6139-7545
	13

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

1 2			
3 4 5	302	Ref	<i>Terences</i>
6 7	303		
8 9	304	1.	Smith SC Jr, Jackson R, Pearson TA, et al. Principles for national and regional guidelines on
10 11	305		cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum.
12 13	306		<i>Circulation</i> 2004;109:3112-21.
14 15	307	2.	Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four
16 17 18	308		racial or ethnic groups. N Engl J Med 2008;358:1336-45.
19 20	309	3.	Erbel R, Möhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and
21 22	310		reclassification improvement based on quantification of subclinical coronary atherosclerosis: the
23 24	311		Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56:1397-406.
25 26	312	4.	Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification:
27 28	313		observations from a registry of 25, 253 patients. J Am Coll Cardiol 2007;49(18):1860-70.
29 30	314	5.	Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause
31 32	315		mortality. JACC Cardiovasc Imaging 2010;3:1229-36.
33 34 35	316	6.	Lehmann N, Erbel R, Mahabadi AA, et al. Value of Progression of Coronary Artery Calcification
36 37	317		for Risk Prediction of Coronary and Cardiovascular Events: Result of the HNR Study (Heinz
38 39	318		Nixdorf Recall). Circulation 2018;137:665-79.
40 41	319	7.	Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham
42 43	320		score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5.
44 45	321	8.	Agarwal S, Cox AJ, Herrington DM, et al. Coronary calcium score predicts cardiovascular
46 47	322		mortality in diabetes: diabetes heart study. Diabetes Care 2013;36:972-7.
48 49	323	9.	Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail
50 51 52	324		2011;17:451-8.
52 53 54	325	10.	Zhang WJ, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell
55 56	326		adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res 2002;55:820-9.
57 58 59 60	327	11.	Wiedermann CJ. Antiinflammatory activity of albumin. <i>Crit Care Med</i> 2007;35:981-2. 14

12. Anraku M, Chuang VT, Maruyama T, et al. Redox properties of serum albumin. Biochim Biophys Acta 2013;1830:5465-72. 13. Paar M, Rossmann C, Nusshold C, et al. Anticoagulant action of low, physiologic, and high albumin levels in whole blood. PLoS One 2017;12:e0182997. 14. Nelson JJ, Liao D, Sharrett AR, et al. Serum albumin level as a predictor of incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:468-77. 15. Shaper AG, Wannamethee SG, Whincup PH. Serum albumin and risk of stroke, coronary heart disease, and mortality: the role of cigarette smoking. J Clin Epidemiol 2004;57:195-202. 16. Djoussé L, Rothman KJ, Cupples LA, et al. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. Circulation 2002;106:2919-24. 17. Yang Q, He YM, Cai DP, et al. Risk burdens of modifiable risk factors incorporating lipoprotein (a) and low serum albumin concentrations for first incident acute myocardial infarction. Sci Rep 2016;6:35463. 18. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging 2009;2:692-700. 19. Han D, Kolli KK, Al'Aref SJ, et al. Machine learning framework to identify individuals at risk of rapid progression of coronary atherosclerosis: From the PARADIGM registry. J Am Heart Assoc 2020;9:e013958. 20. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32. 21. Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an analytical approach that accounts for inter-scan variability. AJR Am J Roentgenol 2004;182:1327-32. 22. Hu H, Sparrow D, Weiss S. Association of serum albumin with blood pressure in the normative aging study. Am J Epidemiol 1992;136:1465-73. 

## BMJ Open

3			
4 5	354	23.	Tell GS, Rutan GH, Kronmal RA, et al. Correlates of blood pressure in community-dwelling older
6 7	355		adults. The Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative
8 9	356		Research Group. Hypertension 1994;23:59-67.
10 11	357	24.	Høstmark AT, Tomten SE, Berg JE. Serum albumin and blood pressure: a population-based, cross-
12 13	358		sectional study. J Hypertens 2005;23:725-30.
14 15	359	25.	Danesh J, Muir J, Wong YK, et al. Risk factors for coronary heart disease and acute-phase proteins.
16 17	360		A population-based study. Eur Heart J 1999;20:954-9.
18 19	361	26.	Ishizaka N, Ishizaka Y, Nagai R, et al. Association between serum albumin, carotid atherosclerosis,
20 21	362		and metabolic syndrome in Japanese individuals. Atherosclerosis 2007;193:373-9.
22 23 24	363	27.	Kunutsor SK, Khan H, Laukkanen JA. Serum albumin concentration and incident type 2 diabetes
24 25 26	364		risk: new findings from a population-based cohort study. Diabetologia 2015;58:961-7.
20 27 28	365	28.	Cho HM, Kim HC, Lee JM, et al. The association between serum albumin levels and metabolic
29 30	366		syndrome in a rural population of Korea. J Prev Med Public Health 2012;45:98-104.
31 32	367	29.	Roche M, Rondeau P, Singh NR, et al. The antioxidant properties of serum albumin. FEBS Lett
33 34	368		2008;582:1783-7.
35 36	369	30.	Djoussé L, Rothman KJ, Cupples LA, et al. Relation between serum albumin and carotid
37 38	370		atherosclerosis: the NHLBI Family Heart Study. Stroke 2003;34:53-7.
39 40	371	31.	Cho I, Al'Aref SJ, Berger A, et al. Prognostic value of coronary computed tomographic
41 42	372		angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective
43 44	373		multicentre international CONFIRM study. <i>Eur Heart J</i> 2018;39:934-41.
45 46	374	32.	Won KB, Park EJ, Han D, et al. Triglyceride glucose index is an independent predictor for the
47 48	375		progression of coronary artery calcification in the absence of heavy coronary artery calcification at
49 50	376		baseline. <i>Cardiovasc Diabetol</i> 2020;19:34.
51 52 53	377	33	Won KB, Han D, Lee JH, <i>et al.</i> Atherogenic index of plasma and coronary artery calcification
54 55	378	55.	progression beyond traditional risk factors according to baseline coronary artery calcium score. <i>Sci</i>
56 57	379		Rep 2020;10:21324.
58 59			16
60			

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

## **Table 1** Baseline characteristics

	Total	Tertiles of serum albumin			
	(n = 12,344)	I (lowest)	Π	III (highest)	Р
		(n = 3,111)	(n = 5,241)	(n = 3,992)	
		3.5–4.2 g/dL	4.3-4.5 g/dL	4.6–5.5 g/dL	
Age, years	51.7 ± 8.5	53.8 ± 8.5	52.1 ± 8.3	49.5 ± 8.3	< 0.00
Male, n (%)	10400 (84.3)	2480 (79.7)	4382 (83.6)	3538 (88.6)	< 0.00
SBP, mmHg	119.6 ± 15.0	$117.3 \pm 15.4$	$119.0 \pm 15.1$	$122.1 \pm 14.3$	< 0.00
DBP, mmHg	75.1 ± 10.6	73.2 ± 10.4	74.6 ± 10.6	77.1 ± 10.3	< 0.00
BMI, kg/m <sup>2</sup>	24.6 ± 2.8	24.5 ± 2.8	24.6 ± 2.7	24.6 ± 2.8	0.142
Hypertension	4024 (33.6)	961 (31.6)	1701 (33.6)	1362 (35.2)	0.007
Diabetes	1699 (13.8)	390 (12.5)	702 (13.4)	607 (15.2)	0.003
Hyperlipidemia	3459 (28.0)	777 (25.0)	1431 (27.3)	1251 (31.3)	< 0.00
Obesity	5191 (42.2)	1285 (41.5)	2192 (42.0)	1714 (43.1)	0.362
Current smoking	3232 (28.5)	851 (29.6)	1341 (28.1)	1040 (28.2)	0.328
Alcohol consumption	7777 (81.3)	2145 (78.1)	3486 (81.9)	2146 (83.5)	< 0.00
Total cholesterol, mg/dL	$197.5 \pm 34.0$	$190.9 \pm 33.2$	197.0 ± 32.8	203.3 ± 35.2	< 0.00
Triglyceride, mg/dL	141.7 ± 89.3	133.2 ± 85.6	140.6 ± 85.2	$149.7 \pm 96.5$	< 0.00
HDL-C, mg/dL	53.3 ± 16.0	52.8 ± 14.2	53.4 ± 16.3	53.6 ± 16.7	0.102
LDL-C, mg/dL	$122.0 \pm 31.7$	$118.8 \pm 30.4$	122.2 ± 31.6	124.2 ± 32.7	< 0.00
Fasting glucose, mg/dL	$97.9 \pm 20.4$	95.7 ± 19.8	97.8 ± 20.7	99.6 ± 20.1	< 0.00
HbA1C, %	5.68 ± 0.74	$5.63 \pm 0.74$	5.66 ± 0.73	5.75 ± 0.74	< 0.00
Creatinine, mg/dL	$0.95 \pm 0.17$	$0.95 \pm 0.17$	$0.95 \pm 0.17$	$0.95 \pm 0.17$	0.471
Albumin, g/dL	$4.44 \pm 0.27$	4.10 ± 0.12	$4.40 \pm 0.08$	4.75 ± 0.16	< 0.00

381 Values are given as the mean  $\pm$  standard deviation or number (%).

BMI, body mass index; DBP, diastolic blood pressure; HbA1C, hemoglobin A1C; HDL-C, high-density
lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

2	
2	
3	
4	
5	
6	
7	
8	
9	
8 9 10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
21 22 23	
∠⊃ ว≀	
24	
25 26	
26	
27	
28	
29	
30	
31	
32	
33	
34	
25	
35 36 37	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
40 47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	

384	Table 2 Baseline and changes of CAC according to serum albumin tertiles
-----	---

	Total	Tertiles of serur			
	(n = 12344)	I (lowest)	II	III (highest)	Р
		(n = 3111)	(n = 5241)	(n = 3992)	
		3.5–4.2 g/dL	4.3–4.5 g/dL	4.6–5.5 g/dL	
Baseline					
Categorical CACS					0.022
0	6937 (56.2)	1738 (55.9)	2930 (55.9)	2269 (56.8)	
1–10	1723 (14.0)	456 (14.7)	772 (14.7)	495 (12.4)	
11–100	2381 (19.3)	575 (18.5)	996 (19.0)	810 (20.3)	
>100	1303 (10.6)	342 (11.0)	543 (10.4)	418 (10.5)	
Follow-up	6				
Categorical CACS					< 0.001
0	5771 (46.8)	1396 (44.9)	2391 (45.6)	1984 (49.7)	
1–10	1054 (8.5)	243 (7.8)	482 (9.2)	329 (8.2)	
11–100	2836 (23.0)	711 (22.9)	1212 (23.1)	913 (22.9)	
>100	2683 (21.7)	761 (24.5)	1156 (22.1)	766 (19.2)	
$\Delta \sqrt{\text{transformed CACS}}$	0 (0-3.46)	0.39 (0-4.62)	0 (0-3.61)	0 (0-2.51)	< 0.001
Annualized $\Delta \sqrt{\text{transformed}}$	0 (0-1.10)	0.16 (0-1.24)	0 (0-1.09)	0 (0-1.01)	< 0.001
CACS					
CAC progression, n (%)					
Overall	3780 (30.6)	1138 (36.6)	1643 (31.3)	999 (25.0)	< 0.001
Categorical CACS					
at baseline					
0	902 (13.0)	271 (15.6)	401 (13.7)	230 (10.1)	< 0.001
1–10	992 (57.6)	299 (65.6)	473 (61.3)	220 (44.4)	< 0.001
11–100	1201 (50.4)	361 (62.8)	499 (50.1)	341 (42.1)	< 0.001

1 2 3 4 5 6 7		>100
6 7	385	Values are
7 8 9 10 11 23 14 15 16 7 8 9 20 21 22 32 4 25 26 7 8 9 30 31 23 34 35 36 7 8 9 0 12 23 24 25 26 7 8 9 30 31 23 34 56 7 8 9 0 12 23 24 25 26 7 8 9 30 31 23 34 56 7 8 9 0 11 22 34 25 26 7 8 9 30 31 23 34 56 7 8 9 0 11 22 3 24 25 26 7 8 9 30 31 23 34 56 7 8 9 0 11 22 3 24 56 7 8 9 30 31 23 34 56 7 8 9 0 11 22 3 24 56 7 8 9 30 31 23 34 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 11 22 33 45 56 7 8 9 0 12 23 24 55 67 8 9 0 12 23 24 55 67 8 9 0 12 23 24 55 67 8 9 0 12 23 24 55 67 8 9 0 12 23 24 55 67 8 9 0 12 23 24 55 67 8 9 0 12 23 34 56 7 8 9 0 12 23 24 55 67 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 56 57 57 57 57 57 57 57 57 57 57 57 57 57	386	CAC, coror

685 (52.6) 207 (60.5) 270 (49.7) 0.003 208 (49.8) given as the mean  $\pm$  standard deviation, the median (interquartile range), or number (%). nary artery calcification; CACS, coronary artery calcium score. to perterior only

	Annualized $\Delta \sqrt{\text{transformed CAC}}$			CAC progression		
	β	SE	p	OR (95% CI)	Р	
Age, pre-1 years increase	0.038	0.002	< 0.001	1.071 (1.066–1.076)	<0	
Male	0.472	0.043	< 0.001	2.628 (2.312-2.987)	<0	
Hypertension	0.514	0.034	< 0.001	2.112 (1.948-2.289)	<0	
Diabetes	0.639	0.046	< 0.001	2.269 (2.044-2.518)	<0	
Hyperlipidemia	0.329	0.035	< 0.001	1.722 (1.585–1.870)	<0	
Obesity	0.259	0.032	< 0.001	1.529 (1.415-1.652)	<0	
Current smoking	0.108	0.037	0.004	1.088 (0.997–1.188)	0.0	
Alcohol consumption	0.099	0.049	0.045	1.218 (1.091–1.360)	<0	
Creatinine, per-1 mg/dL increase	0.827	0.093	< 0.001	4.051 (3.211-5.109)	<0	
Albumin, per-1 g/dL increase	-0.288	0.058	< 0.001	0.442 (0.383-0.510)	<0	
Baseline CACS, per-1 unit	0.001	0.001	< 0.001	1.002 (1.002–1.003)	<0	

CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval;, OR, odds ratio.

Tez oni

## **Table 3** Association of individual clinical factor with CAC changes

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

1 2 3 4	
5 6 7 8	
9 10 11 12 13	
13 14 15 16 17	
18 19 20 21	
22 23 24 25	
26 27 28 29	
30 31 32 33	
34 35 36 37 38	
38 39 40 41 42	
43 44 45 46	
47 48 49 50	
51 52 53 54	
55 56 57 58	
59 60	

**Table 4** Serum albumin levels (per-1 g/dL increase) and the risk of CAC progression according to

## 390 baseline CACS

	OR (95% CI)	Р
Overall		
Model 1	0.583 (0.487-0.696)	<0.001
Model 2	0.578 (0.483-0.691)	<0.001
CACS 0		
Model 1	0.901 (0.649–1.252)	0.535
Model 2	1.051 (0.736–1.502)	0.784
CACS 1–10	Y	
Model 1	0.220 (0.141-0.344)	<0.001
Model 2	0.392 (0.234-0.658)	< 0.001
CACS 11-100		
Model 1	0.286 (0.199–0.409)	<0.001
Model 2	0.580 (0.381-0.883)	0.011
CACS >100		
Model 1	0.360 (0.224-0.579)	<0.001
Model 2	0.688 (0.404-1.170)	0.167

P values for interaction between serum albumin levels and categorical CACS was 0.142.

392 CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; OR, odds ratio.
 393 Models:1 = adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, and alcohol
 394 consumption; 2 = adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol
 395 consumption, serum creatinine levels, baseline CACS, and interscan period.

2		
3 4	396	Figure legend
5 6	397	
7 8 9	398	Figure 1 Subgroup analysis for the association between serum albumin levels and the risk of CAC
9 10 11	399	progression
12 13		
14 15		
16 17		
18 19		
20 21 22		
22 23 24		
25 26		
27 28		
29 30		
31 32		
33 34 35		
36 37		
38 39		
40 41		
42 43		
44 45 46		
47 48		
49 50		
51 52		
53 54		
55 56 57		
57 58 59		22
60		

#### **Supplemental materials**

- Supplementary table 1 Multiple regression models for the association between serum albumin levels
- (per-1 g/dL increase) and the annualized  $\Delta\sqrt{\text{transformed CAC}}$
- Supplementary table 2 Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

or oper teries only

1								
2								
3								
4								
5								
6							_	
7	Age ≥60 years				OR	95% CI	Р	P for interaction
8	No (n = 10,195)				0.549	0.467-0.645	<0.001	0.095
	Yes (n = 2,149)				0.399	0.285-0.559	<0.001	
9	Sex							
10	Male (n = 10,400)		_		0.390	0.335-0.454	<0.001	0.648
11	Female (n = 1,944)	│ — <b>•</b> ─			0.346	0.213-0.564	<0.001	
12	Hypertension							
13	No (n = 7,939)		-		0.370	0.306-0.447	<0.001	0.156
14	Yes (n = 4,024)	-	•		0.459	0.364-0.580	<0.001	
15	Diabetes							
16	No (n = 10,643)		_		0.392	0.334-0.460	<0.001	0.022
17	Yes (n = 1,699)			-   '	0.612	0.433-0.865	0.005	
18	Hyperlipidemia	_						
19	No $(n = 8,885)$				0.350	0.293-0.418	<0.001	0.002
20	Yes (n = 3,459) <b>Obesity</b>				0.574	0.447-0.737	<0.001	
	No (n = 7,104)	_	-		0.451	0.372-0.548	<0.001	0.517
21	Yes (n = 5,191)	_	-		0.410	0.331-0.508	<0.001	0.517
22	Current smoking	-				0.001 0.000		
23	No (n = 8,108)	_	-		0.422	0.353-0.504	<0.001	0.787
24	Yes (n = 3,232)	_			0.403	0.308-0.528	<0.001	
25	Alcohol consumption							
26	No (n = 1,793)				0.653	0.445-0.985	0.029	0.855
27	Yes (n = 7,777)		_ <b>-</b> _		0.628	0.524-0.752	<0.001	
28	c	0.0	0.5	1.0				
29								
30			F	igure 1				
31			•	iguic I				
51			27,77mm	(600		וזס		

37x27mm (600 x 600 DPI)

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Supplementary table 1 Multiple regression models for the association between serum albumin levels

(per-1 g/dL increase) and the annualized  $\Delta \sqrt{\text{transformed CAC}}$ 

	Annualized ∆√transformed CAC					
	β SE <i>p</i>					
Model 1	-0.186	0.076	0.014			
Model 2	-0.196	0.076	0.010			

BMI, body mass index; CAC, coronary artery calcification; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Models:1 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption; 2 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS.

**Supplementary table 2** Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

	Serum albumi	Serum albumin levels		
Variables	β	SE	Р	
SBP, per 1-mmHg increase	0.002	0.001	< 0.001	
DBP, per 1-mmHg increase	0.004	0.001	< 0.001	
Triglyceride, per 1-mg/dL increase	0.001	0.001	< 0.001	
LDL-C, per 1-mg/dL increase	0.001	0.001	<0.001	

DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

# **BMJ Open**

## Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2024-086075.R1
Article Type:	Original research
Date Submitted by the Author:	23-Oct-2024
Complete List of Authors:	Won, Ki-Bum; Chung-Ang University Choi, Su-Yeon ; Seoul National University Hospital, Internal Medicine Chun, Eun Ju; Seoul National University Bundang Hospital Park, Sung Hak; Gangnam Heartscan Clinic Sung, Jidong; Samsung Medical Center Jung, Hae Ok; The Catholic University of Korea Chang, Hyuk Jae; Yonsei University Health System
<b>Primary Subject Heading</b> :	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Cardiac Epidemiology < CARDIOLOGY, PUBLIC HEALTH, Cardiovascular imaging < RADIOLOGY & IMAGING, PREVENTIVE MEDICINE

SCHOLARONE<sup>™</sup> Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our <u>licence</u>.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which <u>Creative Commons</u> licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

terez oni

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies



2		
3 4	-	
5	1	Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification
6 7	2	progression in an asymptomatic population of Korean adults: An observational cohort study
8 9	3	
10 11 12	4	Running title: Serum albumin and CAC progression
12 13 14	5	
15 16	6	Ki-Bum Won <sup>1</sup> , Su-Yeon Choi <sup>2</sup> , Eun Ju Chun <sup>3</sup> , Sung Hak Park <sup>4</sup> , Jidong Sung <sup>5</sup> , Hae Ok Jung <sup>6</sup> , Hyuk-Jae
17 18	7	Chang <sup>7</sup> *
19 20	8	
21 22	9	Affiliations:
23 24	10	<sup>1</sup> Division of Cardiology, Chung-Ang University Gwangmyeong Medical Center, Chung-Ang
25 26	11	University College of Medicine, Gwangmyeong, South Korea
27 28 29	12	<sup>2</sup> Division of Cardiology, Healthcare System Gangnam Center, Seoul National University Hospital,
30 31	13	Seoul, South Korea
32 33	14	<sup>3</sup> Division of Radiology, Seoul National University Bundang Hospital, Seongnam, South Korea
34 35	15	<sup>4</sup> Division of Radiology, Gangnam Heartscan Clinic, Seoul, South Korea
36 37	16	<sup>5</sup> Division of Cardiology, Heart Stroke & Vascular Institute, Samsung Medical Center, Seoul, South
38 39	17	Korea
40 41	18	<sup>6</sup> Division of Cardiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of
42 43	19	Korea, Seoul, South Korea
44 45	20	<sup>7</sup> Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University Health System, Seoul, South
46 47 48	21	Korea
48 49 50	22	
50 51 52	23	Word count: 3319
52 53 54	24	
55 56	25	Correspondence:
57 58 59 60	26	Hyuk-Jae Chang, MD, PhD 1

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Division of Cardiology, Severance Cardiovascular Hospital,

50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea

Tel.: +82(0)2 22288460; Fax: +82(0)2 3932041

Yonsei University College of Medicine,

Yonsei University Health System

E-mail: hjchang@yuhs.ac

Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center,

2	
4	27
5 6	20
7	28
8 9	29
10	30
11 12	
13 14	31
15	32
16 17	33
18	
19 20	
21	
22 23	
24	
25 26	
27	
28 20	
29 30	
31	
32 33	
34	
35 36	
37	
38	
39 40	
41	
42 43	
44	
45 46	
47	
48 49	
50	
51 52	
53	
54	
55 56	
57	
58 59	
59 60	

## 34 ABSTRACT

**Objectives** This study evaluated the association between serum albumin levels and coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminemia at baseline. **Design** Observational cohort study Setting Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single ethnicity, multicenter, and observational registry were analyzed. **Participants** A total of 12344 Korean adults with baseline albumin level of >3.5 g/dL ( $51.7 \pm 8.5$  years; 84.3% male) were included. The median interscan period was 3.0 (2.0-4.8) years. All participants were stratified into three groups based on serum albumin tertile. Primary and secondary outcome measures Association of serum albumin with the risk of CAC progression was analyzed using multivariate logistic regression models with adjustment of interscan period. CAC progression was defined as a square root ( $\sqrt{}$ ) transformed difference between the baseline and follow-up coronary artery calcium score (CACS) ( $\Delta \sqrt{\text{transformed CACS}}$ ) of  $\geq 2.5$ . Annualized  $\Delta \sqrt{\text{transformed CACS}}$  was defined as  $\Delta \sqrt{\text{transformed CACS}}$  divided by interscan period. **Results** With increasing serum albumin tertiles, the annualized  $\Delta\sqrt{\text{transformed CACS (I [lowest]: 0.16)}}$ (0-1.24) vs. II: 0 (0-1.09) vs. III [highest]: 0 (0-1.01)) and the incidence of CAC progression (I: 36.6%) vs. II: 31.3% vs. III: 25.0%) were decreased despite higher prevalence of hypertension, diabetes, and hyperlipidemia (all P < 0.05). Serum albumin levels were inversely related to the annualized  $\Delta\sqrt{\text{transformed CACS}}$  and the risk of CAC progression among overall participants. After adjusting for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine levels, baseline CACS, and interscan period, this inverse association between serum albumin levels (per-1 g/dL increase) and the risk of CAC progression was consistently observed, especially in baseline CACS of 1-10 (odds ratio [OR]: 0.392, 95% confidence interval [CI]: 0.234-0.658) and 11-100 (OR: 0.580, 95% CI: 0.381–0.883) (all P < 0.05). **Conclusions** Serum albumin levels were inversely associated with the risk of CAC progression. This 

BMJ Open

Protected by copyright, includir	-
Jing for uses related to text and data mining	Encoimnement Superiour (ARES)
ıg, Al trai	,
ning, a	•
nd simil	•
lar technologies.	

1 2		
3 4	60	phenomenon was predominantly observed in CACS of 1–100 at baseline.
5 6 7	61	
7 8 9	62	Key Words: albumin; atherosclerosis; coronary artery calcium score
9 10 11	63	
12 13	64	STRENGTHS AND LIMITATIONS OF THIS STUDY
14 15	65	
16 17	66	• Longitudinal study with large sample size analyzing the data of multicenter and observational
18 19	67	cohort registry
20 21		
22 23	68	• Assessment of the association of serum albumin levels with coronary artery calcification (CAC)
24 25	69	progression focusing on the baseline coronary artery calcium score
26 27	70	• Adjustment of traditional risk factors to evaluate independent relationship between serum albumin
28 29	71	levels and the risk of CAC progression
30 31	72	• Difficulty in generalizing the results of current study because of the single-ethnicity participants
32 33		
34 35		
36 37		
38 39		
40 41		
42 43		
44 45		
46 47		
48 49		
50 51		
52		
54		
56		
58		4
52 53 54 55 56 57		4

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

### 

### 73 INTRODUCTION

Atherosclerotic coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide.<sup>1</sup> In asymptomatic populations, the coronary artery calcium score (CACS) has been used to stratify cardiovascular (CV) risk based on the evidence that the CACS provides strong prognostic information across age, sex, and ethnicity.<sup>2–4</sup> Moreover, the progression of coronary artery calcification (CAC) has additive prognostic values beyond traditional risk factors, particularly in the absence of heavy baseline CAC.<sup>5,6</sup> Thus, CACS determined using computed tomography (CT) has a substantial role in assessing CV risk for primary prevention.<sup>7,8</sup>

Albumin is a major protein accounting for more than half of the total serum composition. Previous studies have revealed that serum albumin has several physiological properties, including anti-oxidant, anti-inflammatory, and anti-platelet aggregation activities.<sup>9–13</sup> The normal range of serum albumin levels is defined to be within 3.5-5.5 g/dL in clinical practice. Recent evidence has suggested that low serum albumin levels are strongly associated with the increased risk of CHD and mortality beyond traditional risk factors.<sup>14–17</sup> However, data regarding the association between serum albumin levels and coronary atherosclerotic changes in asymptomatic adults are lacking. In addition, although previous studies have revealed that 1) the absence of CAC confers a low CV event risk<sup>2,18</sup> and 2) clinical risk factors are less predictive for the progression of coronary atherosclerosis compared to the baseline coronary plaque burden,<sup>19</sup> little is known regarding the association of serum albumin levels with the risk of CAC progression according to baseline CAC status. Therefore, the present study aimed to evaluate the association between serum albumin levels and the risk of CAC progression in an asymptomatic population of Korean adults without hypoalbuminemia at baseline.

## **METHODS**

## 96 Study population and design

This study analyzed the data of Korea Initiatives on Coronary Artery Calcification (KOICA) which
is a retrospective, single-ethnicity, multicenter, and observational registry with a self-referral setting for

## **BMJ** Open

asymptomatic subjects who underwent general health checkups at six healthcare centers in South Korea (Severance Cardiovascular Hospital; Samsung Medical Center; Seoul St. Mary's Hospital; Seoul National University Hospital; Seoul National University Bundang Hospital; Gangnam Heartscan Clinic). A total of 93914 patients were enrolled in the registry between 2003 and August 2017. Among these participants, 12353 who underwent at least two CAC scans with available serum albumin level data were identified. After excluding nine patients with hypoalbuminemia (serum albumin level <3.5 g/dL), 12344 were included in the present study. All data were obtained during visits to each healthcare center. Self-reported medical questionnaires were used to obtain information on medical histories. Information on the medical histories of hypertension, diabetes, hyperlipidemia, current smoking, and alcohol consumption status of each participant was systematically collected. Height, weight, and blood pressure were measured during healthcare center visits. Blood pressure was measured using an automatic manometer on the right arm after resting for at least 5 mins. Body mass index (BMI) was calculated as weight (kg)/height (m<sup>2</sup>). All blood samples, including those for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, hemoglobin A1C (HbA1C), albumin, and creatinine were obtained after at least 8 h of fasting and analyzed. Hypertension was defined as systolic blood pressure (SBP)  $\geq$ 140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, previous diagnosis of hypertension, or anti-hypertensive medication. Diabetes was defined as a fasting glucose level of  $\geq$ 126 mg/dL, HbA1C level of  $\geq$ 6.5%, a referral diagnosis of diabetes, or receiving anti-diabetic treatment. Hyperlipidemia was defined as a total cholesterol level of  $\geq$ 240 mg/dL, a referral diagnosis of hyperlipidemia, or receiving anti-hyperlipidemic treatment. Obesity was defined as a BMI of  $\geq 25.0 \text{ kg/m}^2$  following the Korean Society for the Study of Obesity Guidelines. Participants were categorized into three groups based on their serum albumin tertiles.

In this study, CACS was measured based on the scoring system previously described by Agatston et al.<sup>20</sup> The baseline CACS was divided into four groups: CACS of 0, 1–10, 11–100, and >100, respectively. The progression of CAC was defined as a difference  $\geq$ 2.5 between the square roots ( $\sqrt{}$ ) of 

the baseline and follow-up CACS ( $\Delta\sqrt{\text{transformed CACS}}$ ),<sup>5,21</sup> considering interscan variability and the proportion of baseline CACS of 0 (56.2%). Annualized  $\Delta \sqrt{\text{transformed CAC}}$  was defined as  $\Delta\sqrt{\text{transformed CAC divided by interscan period. All computed tomography (CT) scans to assess CAC}$ were obtained using >16-slice multidetector CT scanners (Siemens 16-slice Sensation [Siemens AG, Munich, Germany], Philips Brilliance 256 iCT [Philips Healthcare, Amsterdam, The Netherlands], Philips Brilliance 40 channel MDCT [Philips Healthcare], and GE 64-slice Lightspeed [GE Healthcare] Chicago, IL, USA]). The informed written consent for procedures was obtained from all participants at each of centers. All methods were performed following relevant guidelines and regulations. The appropriate institutional review board of Severance Cardiovascular Hospital approved the study protocol (IRB No: 4-2014-0309).

136 Statistical analysis

Continuous variables are expressed as the mean  $\pm$  standard deviation or the median (interquartile range), and categorical variables are presented as absolute values and percentages. After checking the distribution status of independent variables, the one-way analysis of variance test or the Kruskal-Wallis test was used for continuous variables, and the  $\chi^2$  test or Fisher's exact test was used for categorical variables, as appropriate. Univariable regression analyses were performed to evaluate the relation of clinical variables with 1) annualized  $\Delta\sqrt{\text{transformed CACS}}$  and 2) the risk of CAC progression. Subsequently, multiple logistic regression models were used to assess the association of serum albumin levels with the risk of CAC progression considering the baseline categorical CACS (Model 1, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, and interscan period; Model 2, Model 1 + serum creatinine levels and baseline CACS). The forced entry method was used to enter the independent variables into the multivariable regression analysis. All statistical analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at p <0.05 in all analyses. 

  

# **Patient and public involvement**

**Baseline characteristics** 

RESULTS

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plansof our research.

**Table 1** presents the baseline characteristics of the participants. The mean age of the participants158was  $51.7 \pm 8.5$  years, and 10,400 (84.3%) were men. The mean age decreased with increasing serum159albumin tertiles. In contrast, the mean SBP, DBP, total cholesterol, triglyceride, LDL-C, fasting glucose,160and HbA1C levels increased with increasing serum albumin levels. Similarly, the proportion of male161sex and the prevalence of hypertension, diabetes, hyperlipidemia, and alcohol consumption increased162with increasing serum albumin tertiles. Significant differences were not observed in the HDL-C and163creatinine levels or in the prevalence of obesity and current smoking across the serum albumin tertiles.

# 165 Baseline and changes of CAC according to the serum albumin tertiles

The median interscan period was 3.0 (2.0–4.8) years. During follow-up, the mean changes of  $\sqrt{\text{transformed CACS}}$  and annualized  $\sqrt{\text{transformed CACS}}$  were decreased with increasing serum albumin tertiles. The incidence of the CAC progression in overall participants was 30.6%; it significantly decreased with increasing serum albumin tertiles. The incidence of CAC progression at baseline CACS of 0, 1–10, 11–100, and >100 was 13.0%, 57.6%, 50.4%, and 52.6%, respectively; the progression of CAC was less observed with increasing serum albumin tertiles in all baseline CACS groups (**Table 2**).

# 174 Association between clinical variables and CAC changes

Univariable linear regression analysis showed that age, male sex, hypertension, diabetes,
hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine, and baseline CACS

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

were positively related to the annualized  $\Delta \sqrt{\text{transformed CACS}}$ ; in contrast, serum albumin levels were inversely related to the annualized  $\Delta \sqrt{\text{transformed CACS}}$ . In univariable logistic regression analysis, age, male sex, hypertension, diabetes, hyperlipidemia, obesity, alcohol consumption, serum creatinine level, and baseline CACS were associated with an increased risk of progression of CAC. The results regarding the risk of CAC progression related to glucose, triglyceride, HDL-C, and LDL-C are present in **Supplementary table 1.** Elevated serum albumin levels were associated with a decreased risk of progression of CAC (**Table 3**). The results of the subgroup analysis of the estimated risk of serum albumin levels for CAC progression are presented in Figure 1. 

#### Serum albumin levels and CAC progression according to baseline CACS

In multiple logistic regression models, serum albumin levels were significantly associated with the decreased risk of CAC progression in overall participants. Multiple linear regression models regarding the association between serum albumin levels and the annualized  $\Delta \sqrt{\text{transformed CACS}}$  with consecutive adjustment of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS showed consistent results (Supplementary table 2). According to the categorical CACS at baseline, model 1 showed that serum albumin levels (per-1 g/dL increase) were consistently associated with the risk of CAC progression in participants with baseline CACS of 1–10 (odds ratio [OR]: 0.396, 95% confidence interval [CI]: 0.237–0.662; P <0.001) and 11–100 (OR: 0.603, 95% CI: 0.397–0.915; P = 0.018). In model 2, this association was consistently observed in participants with baseline CACS of 1-10 (OR: 0.392, 95% CI: 0.234–0.658; P <0.001) and 11–100 (OR: 0.580, 95% CI: 0.381–0.883; P = 0.011) (**Table 4**). 

#### **DISCUSSION**

The present study observed that the incidence of CAC progression significantly decreased with increasing serum albumin levels despite a positive relation between serum albumin levels and the prevalence of hypertension, diabetes, and hyperlipidemia in asymptomatic adults without 

## **BMJ** Open

hypoalbuminemia at baseline. An inverse association between serum albumin levels and the risk of progression of CAC was consistently observed after adjusting for confounding factors. Notably, no significant association between serum albumin levels and the risk of progression of CAC was identified in participants with CACS of 0 as well as in those with CACS of >100 at baseline. These results suggest that high serum albumin levels have a protective effect for the progression of CAC in asymptomatic adults, particularly in those with CACS of 1–100 at baseline.

Several studies have reported a positive association between serum albumin levels and metabolic risk factors, such as blood pressure, insulin resistance, and lipid profile.<sup>22-26</sup> A recent cohort study from the Kuopio Ischaemic Heart Disease population found a linear and positive association between serum albumin levels and type 2 diabetes but not improving diabetes risk prediction during a mean follow-up of 20.4 years.<sup>27</sup> Similar to the previous data reported by Danesh et al. in their cross-sectional investigation of individuals with no history of CHD,<sup>25</sup> we observed that serum albumin levels were positively associated with SBP, DBP, and triglyceride and LDL-C levels among our participants without hypoalbuminemia at baseline (Supplementary Table 3). Although the mechanistic pathways for this association between serum albumin and metabolic disorders are unclear, a higher intake of dietary protein reportedly contributes to the positive association between serum albumin levels and metabolic syndrome.<sup>28</sup> Interestingly, despite a positive relation of serum albumin levels with metabolic abnormalities, numerous studies have shown that serum albumin levels are inversely related to the prognosis with a cardioprotective effect.<sup>14–17</sup>

It is well-known that serum albumin has an essential blood anti-oxidant property as well as physiological activities including anti-inflammation and anti-platelet aggregation.<sup>9-13, 29</sup> Based on these findings, several studies have evaluated the relation between serum albumin levels and subclinical atherosclerosis. The NHLBI (National Heart, Lung, and Blood Institute) Family Heart Study reported that lower serum albumin levels were not associated with an increased risk of prevalent carotid atherosclerosis in men or women among 2,072 participants.<sup>30</sup> However, Ishizaka et al. demonstrated somewhat different results that higher serum albumin levels were inversely associated with the 

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

prevalence of early carotid atherosclerosis, although they were positively associated with the prevalence of metabolic syndrome in 8142 Japanese individuals.<sup>26</sup> To our knowledge, there are no studies with a large sample size on the effect of serum albumin levels on coronary atherosclerotic changes, particularly in conditions without hypoalbuminemia. In this study, we observed an independent and inverse association between serum albumin levels and the progression of CAC in 12,344 asymptomatic participants with normal range of serum albumin levels beyond traditional risk factors, particularly in those with baseline CACS of 1–100. This finding suggests that serum albumin has anti-atherogenic effects, irrespective of its positive association with metabolic abnormalities. However, the superior utility of high serum albumin levels for improving CV risk prediction over and above traditional risk factors is questionable. Also, the present study could not evaluate the association of serum albumin levels with non-calcified plaques or vulnerable plaques in coronary arteries because this data is based on the evaluation of CACS performed in asymptomatic adult population. Further large-scale prospective investigations are required to confirm these issues. 

The CONFRIM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) substudy with a mean follow-up of  $5.9 \pm 1.2$  years recently identified that further prognostic benefit was not offered by coronary CT angiography findings over CACS and traditional risk factors in 1,226 asymptomatic adults.<sup>31</sup> Blaha et al.<sup>18</sup> reported that the absence of CAC predicted survival, with 10-year event rates of approximately 1% in 44,052 consecutive asymptomatic patients referred for CAC testing during a mean follow-up of  $5.6 \pm 2.6$  years. Similarly, the MESA (Multi-Ethnic Study of Atherosclerosis) study found consistent results among 6,722 participants during a median follow-up of 3.8 years, irrespective of racial and ethnic differences.<sup>2</sup> In this study, despite the independent and inverse association between serum albumin levels and the progression of CAC in overall participants, this phenomenon was not observed in participants without CAC or those with CACS >100 at baseline. These results indicate that 1) the absence of CAC reflects a low CV risk status, which is less affected by serum albumin levels in asymptomatic populations and 2) it is hard to predict the progression of CAC using specific biomarkers in condition with CACS of >100 at baseline alike 

# **BMJ** Open

The strength of this study is that the risk of CAC progression is assessed in asymptomatic adult population without heavy CAC at baseline. The proportion of CACS >400 was only 2.6% in the present study. According to the HNR (Heinz Nixdorf Recall) study,<sup>6</sup> repeat CT scans after 5 years provided the readjustment of risk attributable to the increased risk in baseline CACS <400. However, although a high CV risk was present in baseline CACS more than 400, additional evaluation of CACS could not add the prognostic value in this condition. Additionally, the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry, baseline coronary plaque burden was the most important factor, when compared with clinical and laboratory factors, in identifying patients at the risk of rapid plaque progression.<sup>19</sup> These findings emphasize the significance of early detecting both the presence of subclinical coronary atherosclerosis and its progression.

previous KOICA studies have suggested.<sup>32,33</sup>

This study had some limitations. First, this study was performed in asymptomatic adult population who voluntarily participated in the health check-ups, which may have resulted in a selection bias. Second, this was a retrospective study, which may have been influenced by unidentified confounders. Third, data on the participants' physical activity was unavailable. Fourth, we could not control the effects of medications for hypertension, diabetes, and hyperlipidemia on the progression of CAC because of the observational design. Fifth, the sample size of baseline CACS >100 was relatively small compared to that of other baseline categorical CACS. Sixth, different CT scanners were used among the participating centers; however, all participants were examined using the same CT scanner with identical ECG-triggering method during the initial and follow-up image acquisitions. Also, CAC progression was defined with the SQRT method, considering interscan variability in the present study.<sup>5,21</sup> Seventh, the present study did not perform the variability analysis based on the strong evidence regarding variability and reproducibility of CACS measurement.<sup>21,34,35</sup> Eighth, we only evaluated the association of the baseline serum albumin levels with CAC progression; any consecutive serum albumin changes during follow-up were not confirmed. Finally, this study included only a Korean population, which may limit generalization. Nevertheless, this study is unique in that we evaluated the association 

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

between serum albumin levels and the risk of CAC progression after considering baseline CAC statusin an asymptomatic Asian population with normal serum albumin levels.

# 284 CONCLUSIONS

The current study observes that serum albumin levels have an independent and inverse association with the progression of CAC despite their positive relation with metabolic abnormalities in asymptomatic adults without hypoalbuminemia, particularly in those with CACS of 1–100 at baseline. Considering the interaction between clinical variables and serum albumin levels regarding the risk of CAC progression in subgroup analysis, further prospective investigations to evaluate the significance of serum albumin levels for subclinical coronary atherosclerosis focusing on diabetes and hyperlipidemia should be necessary.

# 293 Contributiors

Study hypothesis and design: KBW and HJC. Data acquisitions: KBW, SYC, EJC, SHP, JS, HOJ, and
HJC. Statistical analyses: KBW and HJC. Writing of the initial versions of the manuscript: KBW.
Responsible for the overall content as the guarantor: HJC. All authors read, reviewed and provided
feedback for the final manuscript.

41 298 

# 299 Funding

This research was supported by the Korean Medical Device Development Fund grant funded by the Korean government (Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (Project Number: 1711139017).

**Competing interests** 

305 The authors declare no competing interests.

1 2		
3 4	306	
5 6		
7 8	307	Patient and public involvement
9 10	308	Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
10 11 12	309	plans of this research.
12 13 14	310	
15 16	311	Patient consent for publication
17 18	312	Not applicable.
19 20	313	
21 22	314	Ethics approval
23 24	315	This study involves human participants and was approved by the appropriate institutional review board
25 26	316	of Severance Cardiovascular Hospital (IRB No: 4-2014-0309).
27 28	317	
29 30 31	318	Data availability statement
32 33	319	The datasets used and analyzed in the current study are available from the corresponding author upon
34 35	320	reasonable request.
36 37	321	
38 39	322	ORCID iDs
40 41	323	Ki-Bum Won https://orcid.org/0000-0001-5502-9933 Hyuk-Jae Chang https://orcid.org/0000-0002-6139-7545
42 43	324	Hyuk-Jae Chang https://orcid.org/0000-0002-6139-7545
44 45		
46 47		
48		
49 50		
50 51		
52		
53		
54		
55 56		
56 57		
58		
59		14
60		

#### References Smith SC Jr, Jackson R, Pearson TA, et al. Principles for national and regional guidelines on 1. cardiovascular disease prevention: a scientific statement from the World Heart and Stroke Forum. Circulation 2004;109:3112-21. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four 2. racial or ethnic groups. N Engl J Med 2008;358:1336-45. Erbel R, Möhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and 3. reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56:1397-406. 4. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25, 253 patients. J Am Coll Cardiol 2007;49(18):1860-70. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause 5. mortality. JACC Cardiovasc Imaging 2010;3:1229-36. 6. Lehmann N, Erbel R, Mahabadi AA, et al. Value of Progression of Coronary Artery Calcification for Risk Prediction of Coronary and Cardiovascular Events: Result of the HNR Study (Heinz Nixdorf Recall). Circulation 2018;137:665-79. 7. Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5. Agarwal S, Cox AJ, Herrington DM, et al. Coronary calcium score predicts cardiovascular 8. mortality in diabetes: diabetes heart study. Diabetes Care 2013;36:972-7. Argues S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail 9. 2011;17:451-8. 10. Zhang WJ, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res 2002;55:820-9. 11. Wiedermann CJ. Antiinflammatory activity of albumin. Crit Care Med 2007;35:981-2.

Page 17 of 29

1

BMJ Open

2 3			
4 5	351	12.	Anraku M, Chuang VT, Maruyama T, et al. Redox properties of serum albumin. Biochim Biophys
6 7	352		Acta 2013;1830:5465-72.
8 9	353	13.	Paar M, Rossmann C, Nusshold C, et al. Anticoagulant action of low, physiologic, and high
10 11	354		albumin levels in whole blood. PLoS One 2017;12:e0182997.
12 13	355	14.	Nelson JJ, Liao D, Sharrett AR, et al. Serum albumin level as a predictor of incident coronary heart
14 15	356		disease: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:468-
16 17	357		77.
18 19 20	358	15.	Shaper AG, Wannamethee SG, Whincup PH. Serum albumin and risk of stroke, coronary heart
20 21 22	359		disease, and mortality: the role of cigarette smoking. J Clin Epidemiol 2004;57:195-202.
23 24	360	16.	Djoussé L, Rothman KJ, Cupples LA, et al. Serum albumin and risk of myocardial infarction and
25 26	361		all-cause mortality in the Framingham Offspring Study. Circulation 2002;106:2919-24.
27 28	362	17.	Yang Q, He YM, Cai DP, et al. Risk burdens of modifiable risk factors incorporating lipoprotein
29 30	363		(a) and low serum albumin concentrations for first incident acute myocardial infarction. Sci Rep
31 32	364		2016;6:35463.
33 34	365	18.	Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause
35 36	366		mortality. JACC Cardiovasc Imaging 2009;2:692-700.
37 38 20	367	19.	Han D, Kolli KK, Al'Aref SJ, et al. Machine learning framework to identify individuals at risk of
39 40 41	368		rapid progression of coronary atherosclerosis: From the PARADIGM registry. J Am Heart Assoc
42 43	369		2020;9:e013958.
44 45	370	20.	Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using
46 47	371		ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-32.
48 49	372	21.	Hokanson JE, MacKenzie T, Kinney G, et al. Evaluating changes in coronary artery calcium: an
50 51	373		analytical approach that accounts for inter-scan variability. AJR Am J Roentgenol 2004;182:1327-
52 53	374		32.
54 55	375	22.	Hu H, Sparrow D, Weiss S. Association of serum albumin with blood pressure in the normative
56 57 58	376		aging study. Am J Epidemiol 1992;136:1465-73.
58 59 60			16

377 23. Tell GS, Rutan GH, Kronmal RA, *et al.* Correlates of blood pressure in community-dwelling older
adults. The Cardiovascular Health Study. Cardiovascular Health Study (CHS) Collaborative
379 Research Group. *Hypertension* 1994;23:59-67.

5 6

7 8

9

14

18

35

39

52

58

59 60

- 10
  11
  12
  13
  381
  24. Høstmark AT, Tomten SE, Berg JE. Serum albumin and blood pressure: a population-based, crosssectional study. *J Hypertens* 2005;23:725-30.
- 15 382 25. Danesh J, Muir J, Wong YK, *et al.* Risk factors for coronary heart disease and acute-phase proteins.
  16 383 A population-based study. *Eur Heart J* 1999;20:954-9.
- 384 26. Ishizaka N, Ishizaka Y, Nagai R, *et al.* Association between serum albumin, carotid atherosclerosis,
   and metabolic syndrome in Japanese individuals. *Atherosclerosis* 2007;193:373-9.
- 386 27. Kunutsor SK, Khan H, Laukkanen JA. Serum albumin concentration and incident type 2 diabetes
   387 risk: new findings from a population-based cohort study. *Diabetologia* 2015;58:961-7.
- 388 28. Cho HM, Kim HC, Lee JM, *et al.* The association between serum albumin levels and metabolic
  389 syndrome in a rural population of Korea. *J Prev Med Public Health* 2012;45:98-104.
- 31
  32
  390
  39. Roche M, Rondeau P, Singh NR, *et al.* The antioxidant properties of serum albumin. *FEBS Lett*33
  34
  391
  2008;582:1783-7.
- 36 392 30. Djoussé L, Rothman KJ, Cupples LA, *et al.* Relation between serum albumin and carotid
  37 38 393 atherosclerosis: the NHLBI Family Heart Study. *Stroke* 2003;34:53-7.
- 394 31. Cho I, Al'Aref SJ, Berger A, *et al.* Prognostic value of coronary computed tomographic
   395 angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective
   396 multicentre international CONFIRM study. *Eur Heart J* 2018;39:934-41.
- 397 32. Won KB, Park EJ, Han D, *et al.* Triglyceride glucose index is an independent predictor for the
   398 progression of coronary artery calcification in the absence of heavy coronary artery calcification at
   399 baseline. *Cardiovasc Diabetol* 2020;19:34.
- 400 33. Won KB, Han D, Lee JH, *et al.* Atherogenic index of plasma and coronary artery calcification
   401 progression beyond traditional risk factors according to baseline coronary artery calcium score. *Sci* 402 *Rep* 2020;10:21324.

1

2 3		
4 5	403	34. Halliburton SS, Stillman AE, Lieber M, et al. Potential clinical impact of variability in the
6 7	404	measurement of coronary artery calcification with sequential MDCT. AJR Am J Roentgenol
8 9	405	2005;184:643-8.
10 11	406	35. Oudkerk M, Stillman AE, Halliburton SS, et al. Coronary artery calcium screening: current status
12 13	407	and recommendations from the European Society of Cardiac Radiology and North American
14 15 16	408	Society for Cardiovascular Imaging. Eur Radiol 2008;18:2785-807.
$\begin{array}{c} 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 9\\ 40\\ 41\\ 42\\ 43\\ 44\\ 546\\ 47\\ 48\\ 9\\ 50\\ 51\\ 52\\ 35\\ 56\\ \end{array}$		Society for Cardiovascular Imaging. <i>Eur Radiol</i> 2008;18:2785-807.
57 58		18
59 60		Tc

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

# **Table 1** Baseline characteristics

	Total	Tertiles of seru	m albumin		
	(n = 12,344)	I (lowest)	II	III (highest)	Р
		(n = 3,111)	(n = 5,241)	(n = 3,992)	
		3.5–4.2 g/dL	4.3–4.5 g/dL	4.6–5.5 g/dL	
Age, years	51.7 ± 8.5	53.8 ± 8.5	52.1 ± 8.3	49.5 ± 8.3	< 0.00
Male, n (%)	10,400 (84.3)	2,480 (79.7)	4,382 (83.6)	3,538 (88.6)	< 0.00
SBP, mmHg	119.6 ± 15.0	$117.3 \pm 15.4$	$119.0 \pm 15.1$	$122.1 \pm 14.3$	< 0.00
DBP, mmHg	75.1 ± 10.6	$73.2 \pm 10.4$	74.6 ± 10.6	77.1 ± 10.3	< 0.00
BMI, kg/m <sup>2</sup>	24.6 ± 2.8	24.5 ± 2.8	24.6 ± 2.7	24.6 ± 2.8	0.142
Hypertension	4,024 (33.6)	961 (31.6)	1,701 (33.6)	1,362 (35.2)	0.007
Diabetes	1,699 (13.8)	390 (12.5)	702 (13.4)	607 (15.2)	0.003
Hyperlipidemia	3,459 (28.0)	777 (25.0)	1,431 (27.3)	1251 (31.3)	< 0.00
Obesity	5,191 (42.2)	1,285 (41.5)	2,192 (42.0)	1,714 (43.1)	0.362
Current smoking	3,232 (28.5)	851 (29.6)	1,341 (28.1)	1,040 (28.2)	0.328
Alcohol consumption	7,777 (81.3)	2,145 (78.1)	3,486 (81.9)	2,146 (83.5)	< 0.00
Total cholesterol, mg/dL	$197.5 \pm 34.0$	$190.9 \pm 33.2$	197.0 ± 32.8	203.3 ± 35.2	< 0.00
Triglyceride, mg/dL	141.7 ± 89.3	133.2 ± 85.6	$140.6 \pm 85.2$	149.7 ± 96.5	< 0.00
HDL-C, mg/dL	53.3 ± 16.0	52.8 ± 14.2	53.4 ± 16.3	53.6 ± 16.7	0.102
LDL-C, mg/dL	$122.0 \pm 31.7$	$118.8 \pm 30.4$	$122.2 \pm 31.6$	124.2 ± 32.7	< 0.00
Fasting glucose, mg/dL	$97.9\pm20.4$	95.7 ± 19.8	97.8 ± 20.7	99.6 ± 20.1	< 0.00
HbA1C, %	$5.68 \pm 0.74$	$5.63 \pm 0.74$	5.66 ± 0.73	$5.75 \pm 0.74$	< 0.00
Creatinine, mg/dL	$0.95 \pm 0.17$	$0.95 \pm 0.17$	$0.95 \pm 0.17$	$0.95 \pm 0.17$	0.471
Albumin, g/dL	$4.44 \pm 0.27$	4.10 ± 0.12	$4.40 \pm 0.08$	4.75 ± 0.16	< 0.00

410 Values are given as the mean  $\pm$  standard deviation or number (%).

411 BMI, body mass index; DBP, diastolic blood pressure; HbA1C, hemoglobin A1C; HDL-C, high-density
412 lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

1	
2	
3	
4	
5	
6 7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19 20	
20	
21	
22	
23 24	
24	
25 26	
26 27	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

60

413	Table 2 Baseline and changes of CA	C according to serum albumin tertiles
-----	------------------------------------	---------------------------------------

	Total	Tertiles of serur	n albumin		
	(n = 12,344)	I (lowest)	II	III (highest)	Р
		(n = 3,111)	(n = 5,241)	(n = 3,992)	
		3.5–4.2 g/dL	4.3–4.5 g/dL	4.6–5.5 g/dL	
Baseline					
Categorical CACS					0.022
0	6,937 (56.2)	1,738 (55.9)	2,930 (55.9)	2,269 (56.8)	
1–10	1,723 (14.0)	456 (14.7)	772 (14.7)	495 (12.4)	
11–100	2,381 (19.3)	575 (18.5)	996 (19.0)	810 (20.3)	
>100	1,303 (10.6)	342 (11.0)	543 (10.4)	418 (10.5)	
Follow-up	6				
Categorical CACS					< 0.001
0	5,771 (46.8)	1,396 (44.9)	2,391 (45.6)	1,984 (49.7)	
1–10	1054 (8.5)	243 (7.8)	482 (9.2)	329 (8.2)	
11–100	2,836 (23.0)	711 (22.9)	1,212 (23.1)	913 (22.9)	
>100	2,683 (21.7)	761 (24.5)	1,156 (22.1)	766 (19.2)	
$\Delta \sqrt{\text{transformed CACS}}$	0 (0-3.46)	0.39 (0-4.62)	0 (0-3.61)	0 (0-2.51)	< 0.001
Annualized $\Delta \sqrt{\text{transformed}}$	0 (0-1.10)	0.16 (0-1.24)	0 (0-1.09)	0 (0-1.01)	< 0.001
CACS					
CAC progression, n (%)					
Overall	3,780 (30.6)	1,138 (36.6)	1,643 (31.3)	999 (25.0)	< 0.001
Categorical CACS					
at baseline					
0	902 (13.0)	271 (15.6)	401 (13.7)	230 (10.1)	< 0.001
1–10	992 (57.6)	299 (65.6)	473 (61.3)	220 (44.4)	< 0.001
11–100	1201 (50.4)	361 (62.8)	499 (50.1)	341 (42.1)	< 0.001

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

208 (49.8)

0.003

BMJ Open

	Annualized $\Delta \sqrt{\text{transformed CAC}}$		CAC progression		
	β	SE	p	OR (95% CI)	Р
Age, pre-1 years increase	0.038	0.002	< 0.001	1.071 (1.066-1.076)	<0
Male	0.472	0.043	< 0.001	2.628 (2.312-2.987)	<0
Hypertension	0.514	0.034	< 0.001	2.112 (1.948-2.289)	<0
Diabetes	0.639	0.046	< 0.001	2.269 (2.044-2.518)	<0
Hyperlipidemia	0.329	0.035	< 0.001	1.722 (1.585–1.870)	<0
Obesity	0.259	0.032	< 0.001	1.529 (1.415–1.652)	<0
Current smoking	0.108	0.037	0.004	1.088 (0.997-1.188)	0.0
Alcohol consumption	0.099	0.049	0.045	1.218 (1.091–1.360)	<0
Creatinine, per-1 mg/dL increase	0.827	0.093	< 0.001	4.051 (3.211-5.109)	<0
Albumin, per-1 g/dL increase	-0.288	0.058	< 0.001	0.442 (0.383-0.510)	<0
Baseline CACS, per-1 unit increase	0.001	0.001	< 0.001	1.002 (1.002–1.003)	<0

# **Table 3** Association of individual clinical factor with CAC changes

 417 CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; OR, odds ratio.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2	
2	
3	
4	
5	
6	
7	
ß	
9	
-	_
1(	J
1	1
12	2
13	3
14	1
1	-
1.	ן ר
15 16	C
1	7
18	3
18 19 20	9
20	)
2	1
2	
22	2
23	3
23 24	4
2	5
25	5
20 20 20 20 20 30	7
21	' -
28	3
29	9
30	)
3	1
32	2
33	5
	2
34	4
35	5
35 36	5
37	7
38	R
39	
4(	
4	1
42	2
43	3
44	1
4	
46	C
47	1
48	3
49	9
50	
	1
	2
53	3
54	
55	
56	
57	
58	5
59	J

60

1

418 **Table 4** Serum albumin levels (per-1 g/dL increase) and the risk of CAC progression according to

# 419 baseline CACS

	OR (95% CI)	Р
Overall		
Model 1	0.813 (0.671–0.985)	< 0.034
Model 2	0.822 (0.677-0.997)	<0.046
CACS 0		
Model 1	1.001 (0.702-1.426)	0.997
Model 2	1.051 (0.736-1.502)	0.784
CACS 1–10		
Model 1	0.396 (0.237–0.662)	< 0.001
Model 2	0.392 (0.234–0.658)	< 0.001
CACS 11-100		
Model 1	0.603 (0.397-0.915)	0.018
Model 2	0.580 (0.381-0.883)	0.011
CACS >100		
Model 1	0.696 (0.409-1.182)	0.179
Model 2	0.688 (0.404-1.170)	0.167

P values for interaction between serum albumin levels and categorical CACS was 0.142.

421 CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; OR, odds ratio.

422 Models:1 = adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol

423 consumption, and interscan period; 2 = Model 1 + adjusted for serum creatinine levels and baseline CACS.

2 3		
4	424	Figure legend
5 6 7	425	
8 9	426	Figure 1 Subgroup analysis for the association between serum albumin levels (per-1 g/dL increase) and
	426	Figure I Subgroup analysis for the association between serum albumin levels (per-1 g/dL increase) and the risk of CAC progression
55 56 57		
58 59 60		24

2 3		
3		
4 5	428	Supplemental materials
6 7	429	
8 9	430	Supplementary table 1 Univariable linear regression analysis for the risk of CAC progression related
10 11	431	to the levels of glucose, triglyceride, HDL-C, and LDL-C
12 13	432	
14 15	433	Supplementary table 2 Multiple regression models for the association between serum albumin levels
16 17 18	434	(per-1 g/dL increase) and the annualized $\Delta \sqrt{\text{transformed CAC}}$
19 20	435	
21 22	436	Supplementary table 3 Univariable linear regression analysis for the association of serum albumin
23 24	437	levels (per-1 g/dL increase) with and clinical variables
25		
26		
27		
28		
29 30		
31		
32		
33		
34		
35		
36		
37		
38		
39 40		
40		
42		
43		
44		
45		
46		
47 48		
40 49		
50		
51		
52		
53		
54		
55		
56 57		
57 58		
58 59		25

1						
2						
3						
4						
5						
6					-	
7	Age ≥60 years		OR	95% CI	Р	P for interaction
8	No (n = 10,195)	_	0.549	0.467-0.645	<0.001	0.095
9	Yes (n = 2,149)	_ <b>_</b>	0.399	0.285-0.559	<0.001	
	Sex					
10	Male (n = 10,400)		0.390	0.335-0.454	<0.001	0.648
11	Female (n = 1,944)		0.346	0.213-0.564	<0.001	
12	Hypertension					
13	No (n = 7,939)		0.370	0.306-0.447	<0.001	0.156
14	Yes (n = 4,024)	<b>_</b>	0.459	0.364-0.580	<0.001	
15	Diabetes					
16	No (n = 10,643)		0.392	0.334-0.460	<0.001	0.022
17	Yes (n = 1,699)		0.612	0.433-0.865	0.005	
18	Hyperlipidemia	-	0.050	0 000 0 440	-0.004	
19	No $(n = 8,885)$	- <b></b>	0.350	0.293-0.418	<0.001	0.002
20	Yes (n = 3,459) Obesity		0.574	0.447–0.737	<0.001	
	No (n = 7,104)		0.451	0.372-0.548	<0.001	0.517
21	Yes (n = 5,191)	_	0.410	0.331-0.508	<0.001	0.517
22	Current smoking	-	0.410	0.001 0.000		
23	No (n = 8,108)		0.422	0.353-0.504	<0.001	0.787
24	Yes (n = 3,232)	_ <b>-</b> •	0.403	0.308-0.528	<0.001	
25	Alcohol consumption					
26	No (n = 1,793)	<b>-</b>	0.653	0.445-0.985	0.029	0.855
27	Yes (n = 7,777)	_ <b>_</b>	0.628	0.524-0.752	<0.001	
28	l 0.	0 0.5 1	.0			
29						
30		Figur	re 1			
31		i igu	~ -			
51		27,27mm (60		וזס		

37x27mm (600 x 600 DPI)

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Supplementary table 1 Univariable linear regression analysis for the risk of CAC progression related to the levels of glucose, triglyceride, HDL-C, and LDL-C

	CAC progress	CAC progression		
Variables	OR	95% CI	Р	
Glucose, per 1-mg/dL increase	1.013	1.011-1.015	<0.001	
Triglyceride, per 1-mg/dL increase	1.002	1.002-1.003	<0.001	
HDL-C, per 1-mg/dL increase	0.994	0.992-0.997	<0.001	
LDL-C, per 1-mg/dL increase	1.005	1.003-1.006	<0.001	

CAC, coronary artery calcification; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-

C, low-density lipoprotein cholesterol; OR, odds ratio.

# **BMJ** Open

Supplementary table 2 Multiple regression models for the association between serum albumin levels

(per-1 g/dL increase) and the annualized  $\Delta \sqrt{transformed \ CAC}$ 

	Annualized ∆√transformed CAC			
	β	SE	р	
Model 1	-0.186	0.076	0.014	
Model 2	-0.196	0.076	0.010	

BMI, body mass index; CAC, coronary artery calcification; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Models:1 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption; 2 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

**Supplementary table 3** Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

	Serum albumin leve	Serum albumin levels		
Variables	β	SE	Р	
SBP, per 1-mmHg increase	0.002	0.001	< 0.001	
DBP, per 1-mmHg increase	0.004	0.001	< 0.001	
Triglyceride, per 1-mg/dL increase	0.001	0.001	<0.001	
LDL-C, per 1-mg/dL increase	0.001	0.001	< 0.001	

DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.