

# 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

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## ABSTRACT

**Objectives** This study evaluated the association between serum albumin levels and coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminaemia at baseline.

**Design** Observational cohort study.

**Setting** Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single ethnicity, multicentre and observational registry were analysed.

**Participants** A total of 12344 Korean adults with baseline albumin level of  $\geq 3.5$  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 analysed using multivariate logistic regression models with adjustment of interscan period. CAC progression was defined as a square root ( $\sqrt{\phantom{x}}$ ) transformed difference between the baseline and follow-up coronary artery calcium score (CACS) ( $\Delta\sqrt{\text{transformed CACS}}$ ) of  $\geq 2.5$ . Annualised  $\Delta\sqrt{\text{transformed CACS}}$  was defined as  $\Delta\sqrt{\text{transformed CACS}}$  divided by interscan period.

**Results** With increasing serum albumin tertiles, the annualised  $\Delta\sqrt{\text{transformed CACS}}$  (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 hyperlipidaemia (all  $p < 0.05$ ). Serum albumin levels were inversely related to the annualised  $\Delta\sqrt{\text{transformed CACS}}$  and the risk of CAC progression among overall participants. After adjusting for age, sex, hypertension, diabetes, hyperlipidaemia, 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 (OR: 0.392, 95% CI: 0.234 to 0.658) and 11–100 (OR: 0.580, 95% CI: 0.381 to 0.883) (all  $p < 0.05$ ).

**Conclusions** Serum albumin levels were inversely associated with the risk of CAC progression. This

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Longitudinal study with large sample size analysing the data of multicentre and observational cohort registry.
- ⇒ Assessment of the association of serum albumin levels with coronary artery calcification (CAC) progression focusing on the baseline coronary artery calcium score.
- ⇒ Adjustment of traditional risk factors to evaluate independent relationship between serum albumin levels and the risk of CAC progression.
- ⇒ Difficulty in generalising the results of current study because of the single-ethnicity participants.

phenomenon was predominantly observed in CACS of 1–100 at baseline.

## 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 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 antioxidant, anti-inflammatory and antiplatelet 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 with 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 hypoalbuminaemia at baseline.

## METHODS

### Study population and design

This study analysed the data of Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single-ethnicity, multicentre and observational registry with a self-referral setting for asymptomatic subjects who underwent general health checkups at six healthcare centres in South Korea (Severance Cardiovascular Hospital; Samsung Medical Centre; 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 hypoalbuminaemia (serum albumin level <3.5 g/dL), 12344 were included in the present study. All data were obtained during visits to each healthcare centre. Self-reported medical questionnaires were used to obtain information on medical histories. Information on the medical histories of hypertension, diabetes, hyperlipidaemia, current smoking and alcohol consumption status of each participant was systematically collected. Height, weight and blood pressure were measured during healthcare centre 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, haemoglobin A1C (HbA1C), albumin and creatinine were obtained after at least 8 hours of fasting and analysed. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg, previous diagnosis of hypertension or antihypertensive medication. Diabetes was defined as a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, a referral diagnosis of diabetes or receiving antidiabetic treatment. Hyperlipidaemia was defined as a total cholesterol level of ≥240 mg/dL, a referral

diagnosis of hyperlipidaemia or receiving antihyperlipidemic treatment. Obesity was defined as a BMI of ≥25.0 kg/m<sup>2</sup> following the Korean Society for the Study of Obesity Guidelines. Participants were categorised 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 of ≥2.5 between the square roots ( $\sqrt{\phantom{x}}$ ) 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%). Annualised  $\Delta\sqrt{\text{transformed CACS}}$  was defined as  $\Delta\sqrt{\text{transformed CACS}}$  divided by interscan period. All 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 centres. 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±SD or the median (IQR), 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) annualised  $\Delta\sqrt{\text{transformed CACS}}$  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, hyperlipidaemia, 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 (V.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

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

**Table 1** Baseline characteristics

|                           | Total (n=12344) | Tertiles of serum albumin           |                             |                                        | P value |
|---------------------------|-----------------|-------------------------------------|-----------------------------|----------------------------------------|---------|
|                           |                 | I (lowest) (n=3111)<br>3.5–4.2 g/dL | II (n=5241)<br>4.3–4.5 g/dL | III (highest) (n=3992)<br>4.6–5.5 g/dL |         |
| Age, years                | 51.7±8.5        | 53.8±8.5                            | 52.1±8.3                    | 49.5±8.3                               | <0.001  |
| Male, n (%)               | 10400 (84.3)    | 2480 (79.7)                         | 4382 (83.6)                 | 3538 (88.6)                            | <0.001  |
| SBP (mm Hg)               | 119.6±15.0      | 117.3±15.4                          | 119.0±15.1                  | 122.1±14.3                             | <0.001  |
| DBP (mm Hg)               | 75.1±10.6       | 73.2±10.4                           | 74.6±10.6                   | 77.1±10.3                              | <0.001  |
| 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   |
| Hyperlipidaemia           | 3459 (28.0)     | 777 (25.0)                          | 1431 (27.3)                 | 1251 (31.3)                            | <0.001  |
| 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)                            | <0.001  |
| Total cholesterol (mg/dL) | 197.5±34.0      | 190.9±33.2                          | 197.0±32.8                  | 203.3±35.2                             | <0.001  |
| Triglyceride (mg/dL)      | 141.7±89.3      | 133.2±85.6                          | 140.6±85.2                  | 149.7±96.5                             | <0.001  |
| 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±31.7      | 118.8±30.4                          | 122.2±31.6                  | 124.2±32.7                             | <0.001  |
| Fasting glucose (mg/dL)   | 97.9±20.4       | 95.7±19.8                           | 97.8±20.7                   | 99.6±20.1                              | <0.001  |
| HbA1C (%)                 | 5.68±0.74       | 5.63±0.74                           | 5.66±0.73                   | 5.75±0.74                              | <0.001  |
| Creatinine (mg/dL)        | 0.95±0.17       | 0.95±0.17                           | 0.95±0.17                   | 0.95±0.17                              | 0.471   |
| Albumin (g/dL)            | 4.44±0.27       | 4.10±0.12                           | 4.40±0.08                   | 4.75±0.16                              | <0.001  |

Values are given as the mean±SD or number (%).  
 BMI, body mass index; DBP, diastolic blood pressure; HbA1C, haemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

## RESULTS

### Baseline characteristics

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

### 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 annualised  $\sqrt{\text{transformed}}$  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**).

### Association between clinical variables and CAC changes

Univariable linear regression analysis showed that age, male sex, hypertension, diabetes, hyperlipidaemia, obesity, current smoking, alcohol consumption, serum creatinine and baseline CACS were positively related to the annualised  $\Delta \sqrt{\text{transformed}}$  CACS; in contrast, serum albumin levels were inversely related to the annualised  $\Delta \sqrt{\text{transformed}}$  CACS. In univariable logistic regression analysis, age, male sex, hypertension, diabetes, hyperlipidaemia, 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 online supplemental 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

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

|                                                                          |                 | Tertiles of serum albumin           |                             |                                        | P value |
|--------------------------------------------------------------------------|-----------------|-------------------------------------|-----------------------------|----------------------------------------|---------|
|                                                                          | Total (n=12344) | I (lowest) (n=3111)<br>3.5–4.2 g/dL | II (n=5241)<br>4.3–4.5 g/dL | III (highest) (n=3992)<br>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                                                                |                 |                                     |                             |                                        |         |
| 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)                             |         |
| Δ √transformed CACS                                                      | 0 (0–3.46)      | 0.39 (0–4.62)                       | 0 (0–3.61)                  | 0 (0–2.51)                             | <0.001  |
| Annualised Δ √transformed CACS                                           | 0 (0–1.10)      | 0.16 (0–1.24)                       | 0 (0–1.09)                  | 0 (0–1.01)                             | <0.001  |
| 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  |
| >100                                                                     | 685 (52.6)      | 207 (60.5)                          | 270 (49.7)                  | 208 (49.8)                             | 0.003   |
| Values are given as the median (IQR), or number (%).                     |                 |                                     |                             |                                        |         |
| CAC, coronary artery calcification; CACS, coronary artery calcium score. |                 |                                     |                             |                                        |         |

Values are given as the median (IQR), or number (%).

CAC, coronary artery calcification; CACS, coronary artery calcium score.

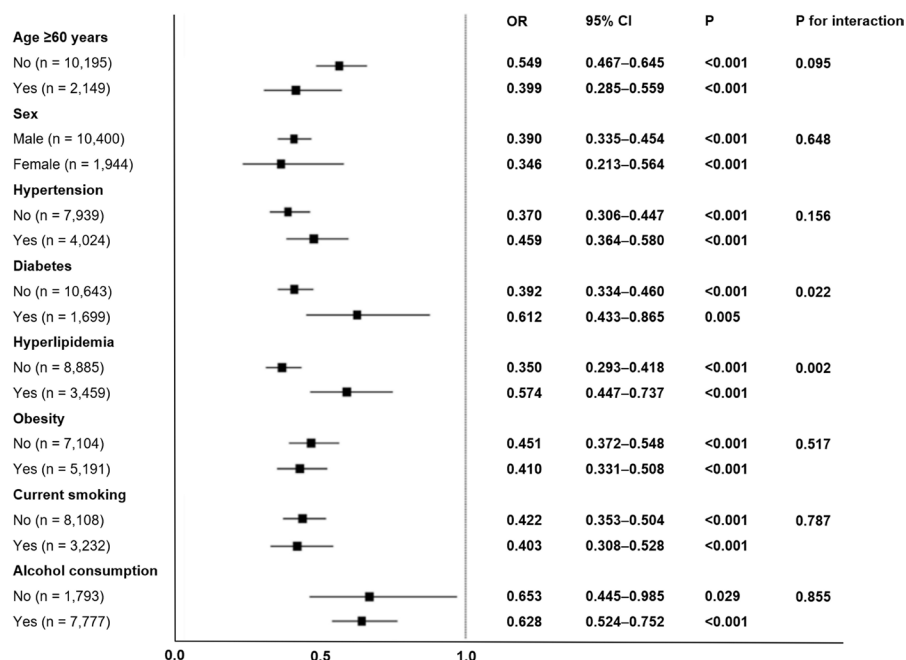
of CAC progression in overall participants. Multiple linear regression models regarding the association between serum albumin levels and the annualised  $\Delta \sqrt{\text{transformed CACS}}$  with consecutive adjustment of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking and

alcohol consumption, serum creatinine levels and baseline CACS showed consistent results (online supplemental 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

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

|                                    | Annualised $\Delta \sqrt{\text{transformed CACS}}$ |       |         | CAC progression        |         |
|------------------------------------|----------------------------------------------------|-------|---------|------------------------|---------|
|                                    | $\beta$                                            | SE    | P value | OR (95% CI)            | P value |
| Age, pre-1 years increase          | 0.038                                              | 0.002 | <0.001  | 1.071 (1.066 to 1.076) | <0.001  |
| Male                               | 0.472                                              | 0.043 | <0.001  | 2.628 (2.312 to 2.987) | <0.001  |
| Hypertension                       | 0.514                                              | 0.034 | <0.001  | 2.112 (1.948 to 2.289) | <0.001  |
| Diabetes                           | 0.639                                              | 0.046 | <0.001  | 2.269 (2.044 to 2.518) | <0.001  |
| Hyperlipidaemia                    | 0.329                                              | 0.035 | <0.001  | 1.722 (1.585 to 1.870) | <0.001  |
| Obesity                            | 0.259                                              | 0.032 | <0.001  | 1.529 (1.415 to 1.652) | <0.001  |
| Current smoking                    | 0.108                                              | 0.037 | 0.004   | 1.088 (0.997 to 1.188) | 0.059   |
| Alcohol consumption                | 0.099                                              | 0.049 | 0.045   | 1.218 (1.091 to 1.360) | <0.001  |
| Creatinine, per-1 mg/dL increase   | 0.827                                              | 0.093 | <0.001  | 4.051 (3.211 to 5.109) | <0.001  |
| Albumin, per-1 g/dL increase       | –0.288                                             | 0.058 | <0.001  | 0.442 (0.383 to 0.510) | <0.001  |
| Baseline CACS, per-1 unit increase | 0.001                                              | 0.001 | <0.001  | 1.002 (1.002 to 1.003) | <0.001  |

CAC, coronary artery calcification; CACS, coronary artery calcium score.;



**Figure 1** Subgroup analysis for the association between serum albumin levels (per-1 g/dL increase) and the risk of CAC progression. CAC, coronary artery calcification.

progression in participants with baseline CACS of 1–10 (OR: 0.396, 95% CI: 0.237 to 0.662;  $p < 0.001$ ) and 11–100 (OR: 0.603, 95% CI: 0.397 to 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 to 0.658;  $p < 0.001$ ) and 11–100 (OR: 0.580, 95% CI: 0.381 to 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 relationship between serum albumin levels and the prevalence of hypertension, diabetes and hyperlipidaemia in asymptomatic adults without hypoalbuminaemia 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

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

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

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

Models: 1 = adjusted for age, sex, hypertension, diabetes, hyperlipidaemia, obesity, current smoking, alcohol consumption and interscan period; 2 = model 1 + adjusted for serum creatinine levels and baseline CACS.

CAC, coronary artery calcification; CACS, coronary artery calcium score.

positively associated with SBP, DBP and triglyceride and LDL-C levels among our participants without hypoalbuminaemia at baseline (online supplemental 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 antioxidant property as well as physiological activities including anti-inflammation and antiplatelet 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 2072 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 the best of 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 hypoalbuminaemia. In this study, we observed an independent and inverse association between serum albumin levels and the progression of CAC in 12344 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 antiatherogenic 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 these data are 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 Multi-centre) substudy with a mean follow-up of  $5.9\pm1.2$  years recently identified that further prognostic benefit was not offered by coronary CT angiography findings over CACS and traditional risk factors in 1226 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 44052 consecutive asymptomatic patients referred for CAC testing during a mean follow-up of

$5.6\pm2.6$  years. Similarly, the MESA (Multi-Ethnic Study of Atherosclerosis) study found consistent results among 6722 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 previous KOICA studies have suggested.<sup>32 33</sup>

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 emphasise the significance of early detecting both the presence of subclinical coronary atherosclerosis and its progression.

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 were unavailable. Fourth, we could not control the effects of medications for hypertension, diabetes and hyperlipidaemia on the progression of CAC because of the observational design. Fifth, the sample size of baseline CACS>100 was relatively small compared with that of other baseline categorical CACS. Sixth, different CT scanners were used among the participating centres; 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 generalisation. 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.

## 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 hypoalbuminaemia, 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 hyperlipidaemia should be necessary.

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