Coronary artery calcium and risk of chronic kidney disease in young and middle-aged adults

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Running title: Coronary artery calcium and chronic kidney disease

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ABSTRACT

Background: The role of coronary artery calcium score (CACS) in incident chronic kidney disease (CKD) in asymptomatic young populations remains unclear. The aim of this study was to evaluate the association between CACS and CKD development in adults.

Methods: A cohort study of 113,171 Korean adults (mean age, 40.6 years) without CKD and proteinuria at baseline, who underwent a cardiac tomography estimation of CACS during health screening examinations, was performed (median follow-up: 4.2 years). The outcome was CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and/or the presence of proteinuria. Hazard ratios (HRs) and 95% confidence intervals (CIs) for CKD were estimated using Cox proportional hazards regression analyses.

Results: A higher CACS was moderately associated with an increased risk of CKD in a dose-dependent manner. The multivariable-adjusted HRs (95% CIs) for CKD comparing CACS 1–100, 101-300, and >300 with CACS=0 were 1.15 (1.05-1.25), 1.37 (1.13-1.66), and 1.71 (1.32-2.22), respectively (*P* for trend <0.001). When CKD was defined using low eGFR and proteinuria separately, corresponding HRs (95% CIs) for low eGFR were 1.31 (1.05-1.62), 1.41 (0.95-2.11), and 1.86 (1.16-3.00), respectively (*P* for trend=0.003), while HR (95% CIs) for proteinuria were 1.11 (1.02-1.21), 1.32 (1.07-1.64), and 1.57 (1.16-2.12), respectively.

Conclusions: A higher CACS was progressively associated with an increased risk of CKD, even at low levels of CACS. Individuals with CACS > 0 appear to have an increased risk of CKD and may benefit from preventive measures to reduce CKD risk.

Keywords: coronary artery calcium score, chronic kidney disease, albuminuria, subclinical atherosclerosis, cohort study

What is already known about this subject?

- Evidence suggests that coronary artery calcium (CAC) is a prevalent condition in individuals with chronic kidney disease (CKD) and is correlated with the severity of CKD.
- The prospective association of CAC scores (CACS) with incident CKD in asymptomatic young adults without clinically detected CKD has not been well documented.

What does this study add?

- A higher CACS was significantly and prospectively associated with increased risk of incident CKD in a dose-response manner in young and middle-aged asymptomatic individuals without CKD at baseline.
- Significantly elevated risk of CKD was observed in individuals elevated CACS , even at low levels and after controlling for potential confounders.

What impact this may have on practice or policy?

- A comparatively low CACS in young adults may still reflect an individual's excess cumulative exposure to shared CVD and CKD risks.
- Individuals with elevated CACS may benefit from appropriate preventive measures to reduce future CKD risk.

INTRODUCTION

Coronary artery calcium (CAC), a reliable measure of coronary atherosclerosis, is a well-established independent predictor of future cardiovascular disease (CVD) events [1, 2]. Accumulating evidence has suggested that CAC can also predict various non-CVD health outcomes, including cancer, chronic pulmonary obstructive disease, dementia, and non-CVD mortality [3-5].

CVD and chronic kidney disease (CKD) are closely related diseases that share multiple common risk factors [6]. Coronary artery disease (CAD) is known to frequently accompany a decline in renal function; in fact, cardiovascular mortality comprises the majority of deaths in CKD patients, accounting for more than 50% of deaths in patients with CKD [6, 7]. There is an increasing recognition that CKD is not only an independent risk factor for CVD, but also a CAD equivalent for all-cause mortality [8]. It is widely recognized that CKD frequently coexists with and promotes CAC progression, and dose-response relationships between severity of CKD and CAC score (CACS) have also been well documented [9-12]. However, existing studies on the effects of CAC in kidney function have been limited to cross-sectional design, small sample sizes and/or relatively narrow patient sample such as those with established CKD or dialysis patients. In addition, scarce evidence exists on whether CAC is prospectively associated with development of CKD in population without impaired renal function [13].

Therefore, we aimed to evaluate the association between CACS and the development of CKD in apparently healthy adults who underwent cardiac tomography estimation of CACSs as part of a routine health screening program.

METHODS

Study population

This study was part of the Kangbuk Samsung Health Study, a cohort study of Korean men and women aged 18 years or above who underwent a comprehensive annual or biennial health examination at the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon, South Korea [14, 15]. Participants were restricted to those who underwent a cardiac CT to measure CACS as part of a comprehensive health examination from January 2010 to December 2018 and had at least one follow-up before December 31, 2020 (n = 122,288). After applying exclusion criteria (see Supplemental Materials), the final analytic sample involved 113,171 participants. This study was conducted in accordance with the practice of the Declaration of Helsinki; the Institutional Review Board of Kangbuk Samsung Hospital approved this study (IRB No. 2021-08-067) and waived the requirement for informed consent due to the use of de-identified data routinely collected as part of the health screening examinations.

Measurements

Data on lifestyle factors, educational level, medical history, and medication were collected by standardized, self-administered questionnaires, while anthropometry and blood pressure were collected by trained nurses, as previously described [14]. For additional details, see Supplementary Materials.

Serum creatinine was measured using the kinetic alkaline picrate (Jaffe) method in an automated chemistry analyzer (Modular D2400, Tokyo, Roche). The within-batch and total coefficients of variation were 1.8 – 3.9% for low level and 1.4 – 1.8% for high-level quality control specimens for the duration of the study. eGFR was calculated using the CKD epidemiology collaboration equation (CKD-EPI). Low GFR was defined as eGFR <60

ml/min/1.73 m^2 according to KDIGO clinical practice guideline [16]. However, as urinary albumin was not measured, CKD was defined for primary analyses as eGFR <60 ml/min/1.73 m^2 and/or the presence of proteinuria in lieu of albuminuria as a marker of kidney damage. Urine protein was determined semi-quantitatively using urine dipsticks (URiSCAN Urine strip, YD Diagnostics, Yong-In, Korea) performed on fresh, midstream urine samples. Urine protein was reported in six grades: absent, trace, 1+, 2+, 3+, and 4+ (corresponding to the following protein levels: undetectable, 10, 30, 100, 300, and 1000 mg/dL, respectively). Proteinuria was defined as grade ≥1+.

CAC was detected with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) in both Seoul and Suwon centers using the same standard scanning protocol [14] of 2.5-mm thickness, 400-ms rotation time, 120-kV tube voltage, and 124-mAS (310 mA × 0.4 s) tube current under ECG-gated dose modulation. CACS were calculated as proposed by Agatston et al. [17] The inter-observer reliability and the intra-observer reliability for CACSs were both excellent (intra-class correlation coefficient of 0.99) [18]. CACSs were defined by the following 4 categories: 0, 1–100, 101-300 and >300 [19, 20].

Statistical analyses

Characteristics of the study participants were presented based on the CACS categories using descriptive statistics, including mean (standard deviation), median (interquartile range), or number (percentage), as appropriate.

The primary endpoint was the development of CKD. Each participant was followed from the time of their baseline examination until either the development of CKD or until their last health examination prior to December 31, 2020, whichever came first. The incidence rate was calculated as the number of incident CKD cases divided by person-years during the follow-up

period. The hazard ratios (HRs) with 95% confidence intervals (CIs) for the development of incident CKD were estimated using Cox proportional hazard models. The proportional hazards assumption was assessed by examining graphs of estimated log (−log (SURVIVAL)); no violation of the assumption was observed.

Data were initially adjusted for age and sex, and were then further adjusted for center, year of screening examination, smoking status, alcohol consumption, regular exercise, BMI, education level, history of diabetes, and history of hypertension (Model 1). Model 2 was further adjusted for lipid-lowering medication, eGFR (for CKD or decreased eGFR), systolic blood pressure, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride, glucose, and HOMA-IR. In additional analyses, regression models were further adjusted for incident hypertension, diabetes, and dyslipidemia during follow-up. We performed a series of sensitivity analyses to test the robustness of our findings including in the competing risk analyses. (For details on supplemental analyses, see Supplementary Materials.)

Statistical analysis was performed using STATA version 16.0 software (StataCorp LP, College Station, TX). All reported P values were two-tailed, with $P < 0.05$ being considered statistically significant.

RESULTS

The mean (standard deviation) age of the 113,171 subjects was 40.6 years (7.2), and the proportion of males was 77.2%. At baseline, 11,036 subjects (9.8%) had CACS between 1 and 100, 1,587 subjects 1.4%) had CACS between 101 – 300, and 372 subjects (0.3%) had CACS >300 (**Table 1**). CACS was positively associated with age, male sex, current smoking status, alcohol intake, regular exercise, obesity, diabetes, hypertension, antidiabetic medication, antihypertensive medication, lipid-lowering medication, worse lipid profiles, liver enzymes,

and higher levels of high-sensitivity C-reactive protein and HOMA-IR; meanwhile, it was inversely associated with eGFR.

During the median follow-up of 4.2 years (interquartile range 2.4-6.3 years; maximum, 9.9 years), 6,044 incident CKD (5,581 proteinuria and 561 low eGFR) were identified (incidence rate, 78.9 per 1,000 person-years). Higher CACS was associated with an increased risk of incident CKD in a dose-response manner, with a significantly increased risk observed even in CAC 1–100 (**Table 2,** *All CKD*). After adjustment for potential confounders, multivariable-adjusted HRs (95% CIs) for incident CKD comparing CACS <0–100, 101-300, and >300 with CACS = 0 were 1.15 (1.05-1.25), 1.37 (1.13–1.66), and 1.71 (1.32-2.22), respectively (*P* for trend <0.001). After additionally controlling for systolic BP, total cholesterol, high density lipoprotein cholesterol, triglyceride, glucose, and HOMA-IR (Model 2), significant associations persisted.

In competing risk analyses where CV and all-cause mortality were considered competing events, the original trends were similarly observed for all CKD and proteinuria, although the associations were slightly attenuated and became non-significant for CKD based on eGFR (**eTable 1**). When the participants were restricted to those who had at least two or three follow-up measurements for eGFR as well as proteinuria in addition to the baseline measurement (**eTable 2**), the associations did not qualitatively change. Of the 5,581 participants who developed proteinuria during follow-up period, 3768 participants had at least one additional follow-up visit of whom 83.9% did not have proteinuria at the subsequent visit. For all definitions of persistent CKD (defined as meeting eGFR or proteinuria criteria for CKD at two consecutive visits), significantly increased risk of persistent CKD was found for CAC <0-100 and CAC 101-300, compared with zero CAC, whereas non-significant increase in the risk was observed in CAC >300, albeit with a significant trend (*P* for trend = 0.003, **eTable 3**).

We have further evaluated the role of incident diabetes, hypertension, and hypercholesterolemia at baseline and during follow-up on the associations between CAC and CKD. For detailed results on the risk of incident diabetes, hypertension, hypercholesterolemia based on CAC categories (**eTable 4**), see Supplementary Material. When incident hypertension, diabetes, and dyslipidemia during follow-up were further adjusted for in evaluating the association between CACS and CKD (**eTable 5**), the associations between CACS and CKD remained virtually unchanged.

eTable 6 presents further exploration of the bidirectional association between CAC and CKD by describing CAC progression in a sample with at least one follow-up measurement of CACS by eGFR values at baseline. The median follow-up duration was 1 year (interquartile range 1-2 years; maximum 9 years). Significantly greater progression rates were found with decreasing baseline eGFR.

In the pre-specified subgroup analyses (**eTable 7**), the association between CACS and incident CKD significantly differed between sexes (women vs. men) (*P* for interaction = 0.009), with associations being significant only in men but not in women, potentially as a consequence of limited power to detect associations in women. No significant interactions were observed in other subgroups.

DISCUSSION

In this large cohort study of 113,171 young and middle-aged adults without CKD at baseline, higher CACS was significantly associated with incident CKD in a dose-response manner. A significantly elevated risk of CKD was observed in individuals with a low level of CACS (1-100), even after controlling for potential confounders including systolic BP, lipid parameters, and inflammatory marker. Our study suggests that even individuals with a low

level of CACS should be considered at risk for CKD and may require early and comprehensive intervention for CKD prevention.

CAC is a prevalent condition in individuals with CKD and is correlated with the severity of CKD [5, 22-25]. However, there is scarce evidence on the role of CACS in incident CKD in asymptomatic individuals without clinically detected CKD. A previous study from the MESA cohort of 6,814 adults examined the role of CAC in non-CVD outcomes, including CKD [5], in which a positive, significant association was found between higher CACS and the risk of incident CKD. However, in that study, the age of the participants was relatively high, with an average of 62.2 years [5]. Moreover, as the CKD cases were determined based on diagnosis codes from inpatient records, there is a possibility of bias towards including only severe disease requiring inpatient management, and CKD history prior to hospitalization was not fully considered in the study [5]. Another recent longitudinal study of 739 patients found that increased CAC in individuals with normal kidney function was associated with a more rapid renal function decline [13]. In the study, the risk of renal outcome, defined by persistent reduction of eGFR, increased only up to CACS <300 and slightly decreased when CACS >300. The study, however, primarily included patients referred for cardiac CT, and the sample sizes may have been limited, especially for CACS ≥ 100, to detect a meaningful association. Therefore, the findings may not be translatable to a younger population without CVD risks or compromised kidney function. Our study is by far the largest study that has examined the relationship of CACS with incident CKD in young and middle-aged population, demonstrating CAC, even at a low level, is associated with increased risk of incident CKD in asymptomatic young adults without known CVD and CKD.

According to the findings from previous cross-sectional studies, the association between CAC and kidney function was largely explained by age or cardiovascular risk factors

[26-28]. In fact, our baseline data suggest that traditional CKD risk factors, such as eGFR, hypertension, and diabetes, increased with higher CACS. Although our study population comprised those initially free of clinically apparent CKD, the presence of CAC may reflect early subclinical decline in kidney function, or so-called "pre-CKD" stage, especially given complex interrelationship between CVD and CKD risk factors. Prior work has largely focused on the role of CKD on development of subclinical atherosclerosis as a consequence of impaired renal function [29, 30]. Our study highlights that CAC may precede incident CKD, and atherosclerotic changes may play a role in the pathogenesis of CKD beyond age or other shared risk factors. With a lack of widely accepted predictive instruments for CKD development and progression, prevention of the progression to full-blown disease warrants the identification of risk factors and early detection of declining renal function [31]. CACS may serve as a tool to stratify at-risk individuals with a high likelihood of developing CKD among asymptomatic adults without clinically apparent CKD, which may have important clinical implications in early CKD prevention.

The mechanism underlying how CAC promotes CKD remains unknown. Several markers of atherosclerosis have been linked to the renal function decline in previous literature. Higher intima-media thickness, a marker of atherosclerotic burden, was associated with accelerated deterioration of renal size and function [32]. Previous studies also support an independent role of arterial stiffness measured by pulse pressure on kidney function decline in population with normal renal function [9, 10]. While mechanistic explanation of how subclinical coronary atherosclerosis as measured by CAC may precede the decline of kidney function has not been well established, CAC may represent increased systemic vascular calcification and thus is likely associated with elevated calcification within the renal vasculature [12]. Glomerular capillaries in the kidney, contrary to other vascular beds, are

particularly sensitive to upstream arterial pulse pressure resulting from atherosclerotic stiffening and are subject to higher pulsatile circumferential stress and longitudinal shear stress, which can have detrimental effects on renal autoregulation [33]. Reduced renal perfusion and disrupted renal hemodynamics due to vascular calcification and arterial stiffness thus can accelerate the decline of renal function [12]. Future investigations should focus on how CAC is specifically involved in the pathogenesis of CKD.

Based on our subgroup analysis, the association between CACS and incident CKD was significant only in men, but not in women. Although the exact mechanism for this is not well understood, gender differences in atherosclerotic risk have been consistently reported in previous work. A recent study showed that males had a 3-fold higher risk of CAC compared to females [34]. While very few studies address whether gender modifies the risk of vascular calcification, especially in relation to CKD, a pervious systematic review of 167 original articles has reported a significantly higher risk of CKD-associated vascular calcification in males [35]. Male gender correlates with a higher risk of atherosclerosis and potentially atherosclerotic calcification [36]. These previous findings may partially explain the higher risk of CKD associated with CAC in men in our study. Several other features that were reported to modify gender related differences include the role of estrogen [37, 38] or differential patterns in calcium and phosphate homeostasis [7, 39], though findings were not consistent across studies. As more than 90% of the groups with prevalent CAC in our study cohort consisted of men, we cannot exclude the possibility that this may have been the result of low statistical power of CACS cases in women. Additional studies are warranted to provide clear mechanistic explanations for the sexual differences observed in our study.

CAC has been widely recognized as a significant predictor of future CVD events and mortality [40]; however, accumulating evidence suggests that CAC also increases the risks of

other non-CVD diseases such as cancer, dementia, or pneumonia, as well as non-CVD mortality [5, 41], highlighting that CAC is not just a marker of CVD-related events but also of overall health of an individual. While the clinical significance of CAC in younger individuals is less clear, evidence suggests that the presence of CAC itself is an abnormal condition in young individuals; indeed, even minimally elevated scores (e.g., as low as 1-10 CAC) in individuals under 45 years of age can be associated with worse prognosis than older individuals [40, 41]. In previous studies, individuals aged <45 years with CACS 1-10 developed markedly higher CVD and non-CVD mortality compared to those with CAC=0 [41-43]. In our study population, with the average age of 41 years, relatively lower levels of CAC (CACS 1-100) represented a significantly higher risk of CKD compared to those with zero CACS. It should be noted that once CAC develops, it will eventually progress at a rate of approximately 20% to 25% per year [44-46]. Also, studies have indicated that CAC = 5 at age 30 may be comparable to CAC~50 at age 40 and CAC~400 at age 50 [46]. In this regard, at a given degree of CAC, younger adults may not only have a greater CVD burden than their older counterparts but also have a greater excess cumulative exposure to CKD risks, given closely interconnected nature of CVD and CKD risk factors. Thus, building on a growing body of literature, our observations confirm that the detection of any amount of CAC at a relatively young age should be of clinical concern. Also, our study adds that interventions aimed at reducing subclinical atherosclerotic burden in these individuals may also be beneficial for future CKD risk reduction.

Our study has several limitations that need to be considered. First, we did not directly measure GFR. However, a direct measure of GFR is considered unsuitable for use in a large-scale clinical study [47]. Second, CKD was identified by a single measurement of eGFR/creatinine or proteinuria at each visit in primary analyses, although clinical diagnostic criteria recommend confirmation by repeated testing. Third, Cystatin C measurements were

not available for the participants, which would have been preferable for small numbers of people with extreme values for muscle mass. Fourth, we were not able to consider changes in CACS in the majority of the study population who only had one assessment of CACS over the duration of follow-up. Fifth, as urine albumin measurement was not available in our study, proteinuria instead of albuminuria was used as a marker of kidney damage. Although measuring albuminuria is a preferred method in defining CKD, proteinuria is an established prognostic marker of CKD [48, 49], and both urine protein-creatinine-ratio and dipstick protein are known to correlate reasonably well with urine albumin measurement [50]. Sixth, the detection of CAC might prompt subsequent healthy lifestyle choices, such as dietary changes and exercise; however, factors related to lifestyle and behavioral modification due to CAC diagnosis were not included in our analyses. However, this would likely have resulted in a bias toward the null. Seventh, factors such as smoking, and alcohol use were assessed using the standard self-administered questionnaire used in the health examination. This may have led to measurement errors for these variables and residual confounding. Eighth, we had no data on specific medications that could affect renal outcome. Nineth, although individuals with decreased eGFR or proteinuria detected during the screening program are referred to clinical evaluation by nephrologists, additional data collected by the clinicians are not available in the screening database. Finally, our study population consisted of relatively highly educated, mostly male, young, and middle-aged Korean adults. Thus, these findings may not be generalizable to older populations, other races/ethnicities, or populations with different sociodemographic characteristics.

Conclusion

Our study of 113,171 young and middle-aged individuals without evidence of CKD at baseline showed that increasing CACS was significantly associated with incident CKD in a

dose-response manner. Our study suggests that elevated CACS even at low level are at increased of CKD and may benefit from preventive measures to reduce future CKD risk.

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Data Availability Statement: The data and study materials will not be made available to other researchers for purposes of reproducing the results. However, analytical methods are available from corresponding author on reasonable request.

Conflict of Interest: All authors declare that they have no conflicts of interest.

Author Contributions

Yejin Kim: interpretation of data, drafting and critical revision of the manuscript

Jeonggyu Kang: interpretation of data, drafting and critical revision of the manuscript

Yoosoo Chang: study concept and design, acquisition of data, interpretation of data, drafting and critical revision of the manuscript

Young Youl Hyun: interpretation of data and critical revision of the manuscript

Kyu-Beck Lee: interpretation of data and critical revision of the manuscript

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Sarah H. Wild: interpretation of data and critical revision of the manuscript

Christopher D Byrne: study concept and design, interpretation of data and critical revision of the manuscript

Seungho Ryu: study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript

All authors confirm that they had full access to all the data

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Table 1. Baseline characteristics of study population based on coronary artery calcification (CAC) score category

Characteristics	Overall	CAC score category				*p* for trend
		0	0< to 100	101 to 300	>300	
Number	113,171	100,176	11,036	1,587	372	
Age (years) [a]	40.6 (7.2)	39.8 (6.6)	46.0 (7.7)	50.1 (8.5)	54.8 (9.8)	<0.001
Male (%)	77.2	75.3	91.8	93.3	93.2	<0.001
Current smoking (%)	22.6	21.5	31.2	34.7	30.3	<0.001
Alcohol intake (%) [c]	25.6	24.3	35.0	38.9	42.5	<0.001
Regular exercise (%) [d]	13.4	13.1	15.7	17.9	21.5	<0.001
High education level (%) [e]	85.4	85.7	84.0	81.0	75.7	<0.001
Diabetes (%)	4.7	3.6	12.0	18.5	27.8	<0.001
Hypertension (%)	14.1	11.6	30.4	45.0	58.0	<0.001
Antidiabetic medication (%)	2.1	1.4	6.1	10.8	19.3	<0.001
Antihypertensive medication (%)	5.9	4.2	16.7	29.5	45.3	<0.001
Lipid-lowering medication (%)	3.5	2.6	9.3	16.7	25.7	<0.001
Obesity (%)[f]	39.0	37.4	50.7	52.2	54.8	<0.001
Body mass index (kg/m^2) [a]	24.4 (3.3)	24.2 (3.3)	25.3 (3.1)	25.4 (3.0)	25.6 (3.1)	<0.001
eGFR (ml/min/1.73 m^2) [a]	100.4 (13)	101.1 (12.8)	95.4 (12.6)	92.8 (12.6)	89.8 (12.5)	<0.001
Uric acid	5.8 (1.4)	5.8 (1.4)	6.1 (1.4)	6.0 (1.4)	5.9 (1.3)	<0.001
Systolic BP (mmHg) [a]	112.2 (12.3)	111.6 (12.1)	116.5 (12.4)	118.1 (12.4)	118.9 (12.6)	<0.001
Diastolic BP (mmHg) [a]	72.8 (9.8)	72.2 (9.6)	76.9 (9.8)	78.0 (9.6)	77.2 (8.8)	<0.001
Glucose (mg/dL) [a]	97.2 (14.7)	96.4 (13.4)	102.6 (20.5)	106.4 (25.2)	110.6 (26.4)	<0.001
Glycated hemoglobin (%)	5.6 (0.5)	5.6 (0.5)	5.8 (0.7)	5.9 (0.8)	6.1 (0.9)	<0.001
Total cholesterol (mg/dL) [a]	198.2 (34.3)	197.1 (33.7)	207.1 (37.1)	203.3 (40.4)	195.0 (41.0)	<0.001
LDL-C (mg/dL) [a]	128.9 (32.0)	127.8 (31.5)	137.9 (34.1)	133.8 (36.5)	126.5 (37.2)	<0.001
HDL-C (mg/dL) [a]	55.5 (14.6)	56 (14.7)	51.8 (13.2)	52.3 (13.4)	52.1 (14.2)	<0.001
Triglycerides (mg/dL) [b]	110 (77-161)	107 (75-157)	132 (94-192)	127 (93-186)	130 (92-188)	<0.001
ALT(U/l) [b]	21 (15-32)	21 (15-31)	24 (18-36)	25 (18-36)	26 (18-36)	<0.001
AST(U/l) [b]	26 (17-43)	25 (16-41)	33 (22-54)	36 (24-58)	36 (24-57)	<0.001
hsCRP (mg/L) [b]	0.5 (0.3-1.0)	0.5 (0.3-1.0)	0.6 (0.3-1.1)	0.6 (0.3-1.1)	0.6 (0.4-1.2)	<0.001

HOMA-IR [b]	1.46 (0.97-2.18)	1.44 (0.97-2.14)	1.62 (1.06-2.48)	1.66 (1.07-2.61)	1.79 (1.1-2.86)	<0.001

Data are expressed as [a] mean (standard deviation), [b] median (interquartile range), or percentage.

[c] ≥20 g of ethanol per day; [d] ≥3 times/week; [e] ≥ college graduate; [f] body mass index ≥ 25 kg/m^2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance. LDL-C, low-density lipoprotein cholesterol

Table 2. Development of chronic kidney disease (CKD) and proteinuria by coronary artery calcification (CAC) score category (n = 113,171)

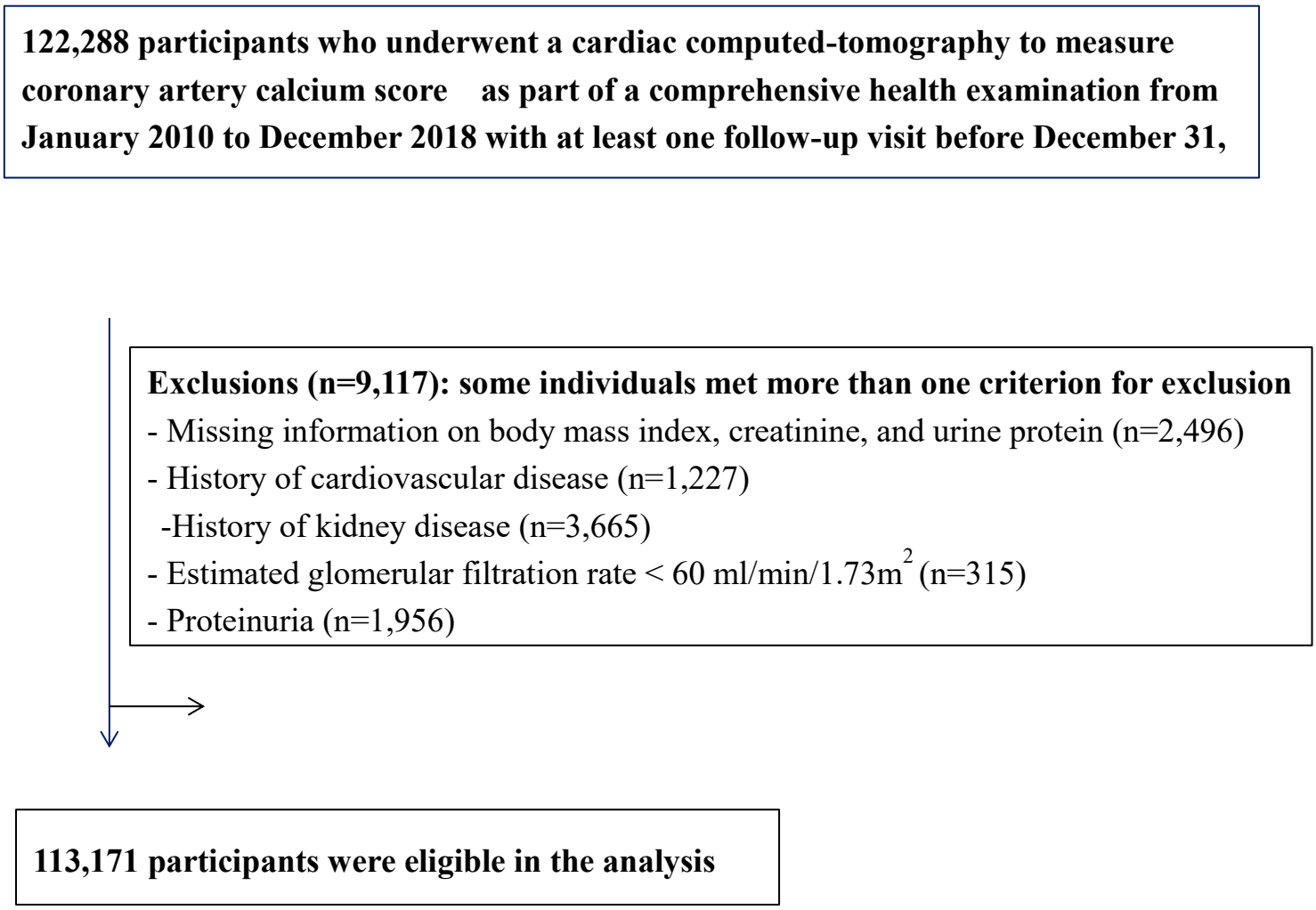
CAC score categories	Person-years (PY)	Incident cases	Incidence rate (per 10^3 PY)	Age-sex adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)	
					Model 1	Model 2
***CKD* eGFR<60[b] as the outcome**						
0	474,782	375	0.79	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	49,791	135	2.71	1.54 (1.25-1.90)	1.31 (1.05-1.62)	1.27 (1.02-1.58)
101 to 300	5,759	29	5.04	1.67 (1.12-2.51)	1.41 (0.95-2.11)	1.42 (0.95-2.12)
>300	2,069	22	10.63	2.03 (1.27-3.24)	1.86 (1.16-3.00)	1.83 (1.14-2.95)
P for trend				<0.001	0.001	0.002
Per 100 increase in CAC score				1.06 (1.01-1.10)	1.02 (0.98-1.07)	1.03 (0.98-1.07)
Proteinuria of ≥1 + grade as the outcome						
0	463,073	4,831	10.43	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	48,441	613	12.65	1.30 (1.19-1.42)	1.11 (1.02-1.21)	1.07 (0.98-1.17)
101 to 300	5,599	92	16.43	1.73 (1.40-2.13)	1.32 (1.07-1.64)	1.26 (1.02-1.56)
>300	2,020	45	22.27	2.39 (1.77-3.23)	1.57 (1.16-2.12)	1.53 (1.13-2.07)
P for trend				<0.001	<0.001	0.001
Per 100 increase in CAC score				1.09 (1.07-1.12)	1.05 (1.02-1.08)	1.05 (1.02-1.09)
Either eGFR <60 [b] or proteinuria as the outcome						
0	462,319	5,143	11.12	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	48,173	726	15.07	1.33 (1.23-1.44)	1.15 (1.05-1.25)	1.11 (1.02-1.20)
101 to 300	5,538	114	20.59	1.77 (1.46-2.14)	1.37 (1.13-1.66)	1.31 (1.08-1.59)
>300	1,974	61	30.90	2.56 (1.98-3.32)	1.71 (1.32-2.22)	1.67 (1.29-2.17)
P for trend				<0.001	<0.001	<0.001
Per 100 increase in CAC score				1.09 (1.07-1.11)	1.06 (1.03-1.08)	1.06 (1.03-1.08)

[a] Estimated from Cox proportional hazard models. Multivariable model 1 was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, and eGFR (for CKD); model 2: model 1 plus adjustment for systolic blood pressure, total cholesterol, HDL-cholesterol, triglyceride, glucose, and HOMA-IR.
[b] ml/min/1.73 m^2
Proteinuria of 1+ grade refers to "30-<100 mg" of protein per dL. Proteinuria was defined as grade ≥1+ one or more times during follow-up period.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; PY, person-years

Figure 1. Flow chart describing the selection of the study participants

Figure 1. Flow chart describing the selection of the study participants



SUPPLEMENTAL MATERIALS

S1. Exclusion criteria

A total of 9,117 participants met one or more of the following exclusion criteria at baseline: missing data on body mass index (BMI), creatinine, and urine protein (n=2,496), a history of CVD (n=1,227), a history of kidney disease (n = 3,665), estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (n = 315), or proteinuria (n = 1,956). As some individuals met more than one exclusion criterion, the final sample of 113,171 participants was included in the analysis.

S2. Measurements

The following data regarding health behaviors and education level were collected: smoking status (never, former, and current smoker), average alcohol consumption (0, ≤20 and >20 g/day), regular exercise (<3 times/week vs. ≥3 times/week), and education level (less than a college degree or greater or equal to a college degree). A family history of CVD was defined as a self-reported diagnosis of heart disease or stroke in one or more first-degree relatives.

Blood samples were obtained after a fasting period of at least 10 hours. The blood tests included lipid profiles, liver enzymes, glucose, insulin, high-sensitivity C-reactive protein, and creatinine. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (mg/dL) × fasting glucose (mg/dL) / 405.

S3. Statistical analyses: subgroup analyses

Subgroup analyses were performed stratified by age (<45 vs. ≥45 years), sex (women vs. men), current smoking (no vs. yes), alcohol intake (< 20 vs. ≥ 20 g/day), health enhancing

physical activity (no vs. yes), BMI (<25 kg/m^2 vs. ≥ 25 kg/m^2), HOMA-IR (<2.5 vs. ≥2.5), and hsCRP (<1.0 mg/L vs. ≥ 1.0 mg/L), diabetes at baseline (no vs. yes), antidiabetic medication (no vs. yes), hypertension at baseline (no vs. yes), and antihypertensive medication (no vs. yes). The interactions by subgroup characteristics were tested using likelihood ratio tests comparing models with and without multiplicative interaction terms.

S3-1. Statistical analyses: competing risk analyses

To account for the competing risks of CVD and all-cause mortality, HRs and 95% CIs for mortality were estimated using the Fine and Gray proportional hazards regression model with age as the timescale.[1]

S3-2. Statistical analyses: annual CAC progression

To estimate the progression of CAC scores over time in the exposure subgroup, we used linear mixed models with random intercepts and slopes with adjustment for potential confounders. Analyses were performed after the transformation of CAC scores to $\log_e$(CAC+1) because the CAC score was right-skewed. Then, the ratios of the annual progression rates of CAC scores (with 95% CIs) were estimated, comparing each eGFR subgroup category with the reference group (normal group). These analyses of CAC progression were performed in all participants and then separately in those with CAC scores of zero and CAC>0 at baseline. Since participants had to have at least two visits, we used inverse probability weights to correct for potential selection bias between participants with a single CAC measurement and those with two or more CAC measurements. Inverse probability weights were obtained from a logistic regression model that included all participants with at least one CAC measurement. Multivariable models were adjusted for smoking status, alcohol consumption, regular exercise,

body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-C, triglyceride, glucose, and HOMA-IR as time-dependent variables and age at baseline, sex, center, year of screening examination, and education level as time-fixed variables.

S4. Results: the role of incident diabetes, hypertension, and hypercholesterolemia

We have further evaluated the role of incident diabetes, hypertension, and hypercholesterolemia at baseline and during follow-up on the associations between CAC and CKD. Over the course of follow-up, the incident cases of hypertension, diabetes, and dyslipidemia (defined as serum LDL cholesterol ≥160 mg/dL, serum triglycerides ≥150 mg/dL, or serum HDL cholesterol <40 mg/dL (men) or <50 mg/dL (women))[2] were 33,517 (29.6%), 5,353 (4.7%), and 48,260 (42.6%), respectively. The association between CACS and incident hypertension in individuals without CKD, proteinuria, or hypertension at baseline showed a positive association with a dose-response pattern (**eTable 4**). The HRs (95% CI) for incident hypertension for CACS 0, <0-100, 101-300, and >300 were 1.16 (1.11-1.21), 1.10 (0.95-1.26), and 1.42 (1.14-1.77), respectively. A similar pattern was found for incident diabetes, whereas an inverse J-shaped association was observed between increasing CACS and incident dyslipidemia such that the risk increased in CACS <0-100 which then decreased in higher CACS categories. Additionally, when incident hypertension, diabetes, and dyslipidemia during follow-up were further adjusted for in evaluating the association between CACS and CKD (**eTable 5**), the associations between CACS and CKD remained virtually unchanged.

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eTable 1. Hazard ratios (95% CI) for chronic kidney disease (CKD) and proteinuria according to coronary artery calcium score (CACS) category using competing risk analysis

CACS categories	Sub-distribution HR[a] (95% CI) while considering CV mortality as a competing event			Sub-distribution HR[a] (95% CI) while considering all-cause mortality as a competing event		
	For CKD (eGFR<60 ml/min/1.73 m^2)	For proteinuria	For all CKD (either eGFR <60 ml/min/1.73 m^2 or proteinuria)	For CKD (eGFR<60 ml/min/1.73 m^2)	For proteinuria	For all CKD (either eGFR <60 ml/min/1.73 m^2 or proteinuria)
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	1.22 (0.98-1.51)	1.07 (0.98-1.17)	1.10 (1.01-1.19)	1.21 (0.97-1.50)	1.07 (0.98-1.17)	1.10 (1.01-1.19)
101 to 300	1.14 (0.74-1.75)	1.26 (1.01-1.56)	1.29 (1.06-1.56)	1.10 (0.71-1.70)	1.23 (0.99-1.53)	1.26 (1.04-1.53)
>300	1.23 (0.76-1.99)	1.49 (1.09-2.03)	1.61 (1.23-2.10)	1.16 (0.71-1.90)	1.45 (1.06-1.98)	1.57 (1.20-2.05)
P for trend	0.164	0.002	<0.001	0.248	0.004	<0.001
Per 100 increase in CAC score	1.02 (0.97-1.06)	1.05 (1.02-1.08)	1.05 (1.03-1.08)	1.01 (0.96-1.06)	1.05 (1.02-1.08)	1.05 (1.03-1.08)

[*] Fine and Gray proportional hazard model with age as a time scale was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariable model was adjusted for age (timescale), sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-C, triglyceride, glucose, and HOMA-IR.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio

eTable 2. Hazard ratios (95% CI) for chronic kidney disease (CKD) and proteinuria according to coronary artery calcium score (CACS) category among subjects who had at least two or three follow-up

CACS categories	Multivariable-adjusted HR[a] (95% CI) among subjects who had at least two follow-up (n = 91,288)			Multivariable-adjusted HR[a] (95% CI) among subjects who had at least three follow-up (n = 68,942)		
	For CKD (eGFR<60 ml/min/1.73 m^2)	For proteinuria	For all CKD (either eGFR <60 ml/min/1.73 m^2 or proteinuria)	For CKD (eGFR<60 ml/min/1.73 m^2)	For proteinuria	For all CKD (either eGFR <60 ml/min/1.73 m^2 or proteinuria)
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	1.28 (1.02-1.60)	1.07 (0.97-1.17)	1.10 (1.01-1.20)	1.30 (1.02-1.64)	1.08 (0.98-1.19)	1.12 (1.02-1.22)
101 to 300	1.39 (0.89-2.17)	1.21 (0.97-1.52)	1.26 (1.03-1.54)	1.58 (0.98-2.56)	1.23 (0.97-1.57)	1.27 (1.02-1.59)
>300	1.54 (0.89-2.65)	1.40 (1.002-1.96)	1.51 (1.12-2.02)	1.74 (0.97-3.11)	1.45 (1.01-2.08)	1.55 (1.13-2.14)
P for trend	0.013	0.010	<0.001	0.004	0.006	<0.001
Per 100 increase in CAC score	1.02 (0.98-1.07)	1.05 (1.02-1.08)	1.05 (1.02-1.08)	1.04 (0.99-1.10)	1.06 (1.02-1.09)	1.06 (1.03-1.09)

[a] Estimated from Cox proportional hazard models with inverse probability weighting. Multivariable model was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-C, triglyceride, glucose, and HOMA-IR.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio

eTable 3. Hazard ratios (95% CI) for persistent chronic kidney disease (CKD) and persistent proteinuria according to coronary artery calcium score (CACS) category among subjects who had at least two follow-up (n = 91,288)

CACS categories	For persistent CKD (eGFR<60 ml/min/1.73 m^2)		For persistent proteinuria		For all persistent CKD (either eGFR <60 ml/min/1.73 m^2 or proteinuria)	
	Incident case	Multivariable-adjusted HR[a] (95% CI)	Incident case	Multivariable-adjusted HR[a] (95% CI)	Incident case	Multivariable-adjusted HR[a] (95% CI)
0	72	1.00 (reference)	557	1.00 (reference)	625	1.00 (reference)
<0 to 100	36	1.77 (1.14-2.73)	104	1.22 (0.97-1.52)	135	1.27 (1.04-1.56)
101 to 300	8	1.96 (0.90-4.30)	16	1.32 (0.79-2.21)	26	1.60 (1.06-2.41)
>300	4	1.50 (0.50-4.53)	6	1.25 (0.55-2.85)	10	1.45 (0.76-2.76)
P for trend		0.033		0.070		0.003
Per 100 increase in CAC score		1.03 (0.94-1.14)		1.06 (0.99-1.14)		1.06 (1.01-1.12)

[a] Estimated from Cox proportional hazard models with inverse probability weighting. Multivariable model was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-cholesterol, triglyceride, glucose, and HOMA-IR at baseline as well as incident hypertension, incident diabetes and incident dyslipidemia during follow up.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio

eTable 4. Hazard ratios (95% CI) for hypertension, diabetes or dyslipidemia according to coronary artery calcium score category among subjects without CKD and proteinuria as well as each outcome at baseline

CACS categories	Multivariable-adjusted HR[a] (95% CI) for hypertension among subjects without CKD, proteinuria and hypertension at baseline	Multivariable-adjusted HR[a] (95% CI) for diabetes among subjects without CKD, proteinuria and diabetes at baseline	Multivariable-adjusted HR[a] (95% CI) for dyslipidemia among subjects without CKD, proteinuria and dyslipidemia at baseline	Multivariable-adjusted HR[a] (95% CI) for lipid-lowering medication among subjects without CKD, proteinuria and lipid-lowering medication at baseline
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	1.16 (1.11-1.21)	1.11 (1.03-1.20)	1.13 (1.08-1.18)	1.17 (1.11-1.24)
101 to 300	1.10 (0.95-1.26)	1.24 (1.04-1.47)	0.85 (0.75-0.96)	1.58 (1.42-1.77)
>300	1.42 (1.14-1.77)	1.30 (1.003-1.68)	0.64 (0.52-0.79)	1.63 (1.38-1.93)
P for trend	<0.001	<0.001	0.957	<0.001
Per 100 increase in CAC score	1.05 (1.03-1.08)	1.05 (1.02-1.08)	0.93 (0.90-0.95)	1.04 (1.02-1.05)

[a] Estimated from Cox proportional hazard models with inverse probability weighting. Multivariable model was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes (except for diabetes), history of hypertension (except for hypertension), lipid-lowering medication (except for dyslipidemia and lipid-lowering medication), eGFR, systolic blood pressure (except for hypertension), total cholesterol (except for dyslipidemia), HDL-C (except for dyslipidemia), triglyceride (except for dyslipidemia), glucose (except for diabetes), and HOMA-IR.

Dyslipidemia was defined as serum LDL cholesterol ≥160 mg/dl, serum triglycerides ≥150 mg/dl, or serum HDL cholesterol <40 mg/dl (men) or <50 mg/dl (women).

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio

eTable 5. Hazard ratios (95% CI) for chronic kidney disease (CKD) and proteinuria according to coronary artery calcium score (CACS) category after further adjustment for incident hypertension, incident diabetes and incident dyslipidemia during follow up

CACS categories	Multivariable-adjusted HR[a] (95% CI)		
	For CKD (eGFR<60 ml/min/1.73 m^2)	For proteinuria	For all CKD (either eGFR <60 ml/min/1.73 m^2 or proteinuria)
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	1.26 (1.01-1.57)	1.05 (0.96-1.15)	1.09 (1.01-1.19)
101 to 300	1.40 (0.94-2.10)	1.25 (1.01-1.55)	1.30 (1.07-1.57)
>300	1.80 (1.12-2.91)	1.53 (1.13-2.06)	1.67 (1.29-2.17)
P for trend	0.003	0.002	<0.001
Per 100 increase in CAC score	1.03 (0.98-1.07)	1.05 (1.02-1.08)	1.06 (1.03-1.08)

[a] Estimated from Cox proportional hazard models with inverse probability weighting. Multivariable model was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-cholesterol, triglyceride, glucose, and HOMA-IR at baseline as well as incident hypertension, incident diabetes and incident dyslipidemia during follow up.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio

eTable 6. Ratios* (95% CI) of annual progress rates of coronary artery calcium (CAC) scores by stage of chronic kidney disease (CKD) at baseline (n = 42,681)

	eGFR (ml/min/1.73 m^2)		
	<60	60-89	≥90
Number	95	12,267	30,319
Annual rates of CAC progression	1.198 (1.134–1.266)	1.102 (1.097–1.107)	1.077 (1.074–1.079)
Ratio of annual progression rate			
Model 1	1.113 (1.053–1.176)	1.024 (1.019–1.029)	1.000 (reference)
Model 2	1.121 (1.058–1.188)	1.023 (1.018–1.029)	1.000 (reference)

*Annual CAC progression rates and ratios were estimated from mixed models with random intercepts and slopes with natural log(CAC + 1) as the outcome and inverse probability weighting

Multivariable model 1 was adjusted for age at baseline and sex. Model 2 was adjusted for smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-C, triglyceride, glucose, and HOMA-IR as time-dependent variables and age at baseline, sex, center, year of screening examination, and education level as time-fixed variables.

Abbreviation: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance

eTable 7. Hazard ratio (95% CI) of incident chronic kidney disease (CKD) based on coronary artery calcification (CAC) score category in clinically relevant subgroups

Subgroup	Coronary artery calcification (CAC) score category				*P* for trend	*P* for interaction
	0	0< to 100	101 to 300	>300		
Age						0.551
<45 years (n=86,470)	1.00 (reference)	1.14 (1.03-1.27)	1.29 (0.94-1.78)	1.20 (0.66-2.18)	0.003	
≥45 years (n=26,701)	1.00 (reference)	1.09 (0.96-1.24)	1.36 (1.07-1.73)	1.86 (1.39-2.48)	<0.001	
Sex						0.009
Women (n=25,808)	1.00 (reference)	0.71 (0.53-0.95)	1.17 (0.62-2.19)	0.80 (0.26-2.51)	0.136	
Men (n=87,363)	1.00 (reference)	1.15 (1.06-1.25)	1.37 (1.13-1.65)	1.78 (1.30-2.44)	<0.001	
Current smoking						0.827
No (n=83,802)	1.00 (reference)	1.09 (0.98-1.21)	1.21 (0.93-1.56)	1.73 (1.25-2.39)	0.001	
Yes (n=24,509)	1.00 (reference)	1.11 (0.97-1.28)	1.44 (1.06-1.94)	1.61 (1.02-2.53)	0.002	
Alcohol intake						0.256
<20 g/day (n=80,255)	1.00 (reference)	1.12 (1.01-1.24)	1.46 (1.15-1.86)	1.59 (1.11-2.29)	<0.001	
≥20 g/day (n=27,617)	1.00 (reference)	1.08 (0.94-1.24)	0.95 (0.67-1.36)	1.71 (1.15-2.53)	0.051	
HEPA						0.708
No (n=96,029)	1.00 (reference)	1.11 (1.01-1.21)	1.24 (0.99-1.54)	1.56 (1.15-2.12)	<0.001	
Yes (n=14,885)	1.00 (reference)	1.04 (0.84-1.28)	1.29 (0.82-2.05)	2.12 (1.24-3.62)	0.025	
BMI						0.282
<25 kg/m^2 (n=69,034)	1.00 (reference)	1.10 (0.96-1.25)	1.40 (1.04-1.90)	2.24 (1.53-3.33)	<0.001	
≥25 kg/m^2 (n=44,137)	1.00 (reference)	1.11 (1.00-1.23)	1.25 (0.98-1.60)	1.39 (0.98-1.96)	0.002	
HOMA-IR						0.412
<2.5 (n=92,361)	1.00 (reference)	1.14 (1.03-1.26)	1.46 (1.15-1.83)	1.65 (1.16-2.36)	<0.001	
≥2.5 (n=20,810)	1.00 (reference)	1.05 (0.91-1.20)	1.09 (0.79-1.51)	1.68 (1.16-2.44)	0.034	
hsCRP						0.940
<1.0 mg/L (n=81,687)	1.00 (reference)	1.08 (0.97-1.19)	1.33 (1.05-1.69)	1.70 (1.22-2.38)	<0.001	
≥1.0 mg/L (n=28,945)	1.00 (reference)	1.13 (0.99-1.29)	1.39 (1.01-1.92)	1.60 (1.04-2.47)	0.002	
Diabetes						0.482
No (n=107,818)	1.00 (reference)	1.09 (0.99-1.19)	1.26 (0.99-1.59)	1.54 (1.07-2.20)	0.002	
Yes (n=5,353)	1.00 (reference)	1.21 (1.02-1.45)	1.50 (1.08-2.08)	1.98 (1.36-2.88)	<0.001	
Antidiabetic medication						0.537
No (n=110,540)	1.00 (reference)	1.12 (1.03-1.22)	1.25 (1.00-1.56)	1.75 (1.28-2.39)	<0.001	
Yes (n=2,333)	1.00 (reference)	1.07 (0.83-1.38)	1.66 (1.13-2.45)	1.53 (0.95-2.46)	0.010	

Antihypertensive medication						0.666
No (n=106,209)	1.00 (reference)	1.12 (1.02-1.23)	1.40 (1.10-1.78)	1.96 (1.37-2.82)	<0.001	
Yes (n=6,664)	1.00 (reference)	1.14 (0.95-1.36)	1.26 (0.92-1.71)	1.46 (1.01-2.13)	0.012	
Hypertension						0.654
No (n=97,224)	1.00 (reference)	1.07 (0.96-1.19)	1.24 (0.92-1.67)	1.54 (0.96-2.49)	0.020	
Yes (n=15,946)	1.00 (reference)	1.18 (1.04-1.34)	1.38 (1.07-1.76)	1.76 (1.30-2.40)	<0.001	
Examination time						0.060
Morning (n=100,946)	1.00 (reference)	1.10 (0.85-1.42)	2.56 (1.53-4.29)	2.05 (0.85-4.96)	0.024	
Afternoon (n=12,183)	1.00 (reference)	1.09 (1.00-1.19)	1.21 (0.99-1.48)	1.61 (1.23-2.12)	0.024	

[a] Estimated from Cox proportional hazard models. Multivariable model 1 was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, lipid-lowering medication, eGFR, systolic blood pressure, total cholesterol, HDL-cholesterol, triglyceride, glucose, and HOMA-IR.

Abbreviations: ASM, appendicular skeletal muscle; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein

September 8, 2022

Professor Denis Fouque

Editor-in-Chief

Nephrology Dialysis Transplantation

Dear Prof. Fouque:

Thank you for your constructive suggestions regarding our manuscript NDT-00464-2022.R1 entitled, "**Coronary artery calcium and risk of chronic kidney disease in young and middle-aged adults**." We have revised the manuscript according to the reviewers' recommendations and comments. We believe that our manuscript has improved through this review process. We are pleased to submit the revised version of the manuscript for publication in *Nephrology Dialysis Transplantation*.

In addition to the revised version of the manuscript and signed COI documents, we have uploaded a version with additions underlined in red and deletions crossed out in blue, reflecting the modifications to the manuscript, as well as our point-by-point responses to the reviewers' comments, which detail the changes made in response to the comments.

The authors declare no conflicts of interest related to this manuscript, including financial conflicts. The manuscript has not been submitted for publication elsewhere and is not under consideration by any other journal.

Thank you for your consideration of our manuscript. Please feel free to contact me if you have any questions related to our manuscript. We look forward to hearing from you.

Sincerely,

Seungho Ryu, MD, PhD

Professor of Occupational and Environmental Medicine

Kangbuk Samsung Hospital

Sungkyunkwan University

Reviewers' Comments to Author:

Reviewer: 1

Comments to the Author

I was not able to find the point by point response to the Reviewers' comments, but the revised document with track changes shows that the authors have answered all my queries satisfactorily.

Response: We would like to thank the reviewer for his/her supportive comments, which helped improve the manuscript.

Reviewer: 3

Comments to the Author

The authors adequately addressed all issues.

Response: We would like to thank the reviewer for his/her supportive comments, which helped improve the manuscript.

Reviewer: 2

Comments to the Author

Dear authors,
I appreciate your efforts in answering all the comments. However, I still struggle with the approach to come to the diagnosis "CKD" based on proteinuria.
I acknowledge that you mention lacking UACR as a limitation but estimate a high percentage of proteinuria findings being albuminuria. As approx. 90% of the CKD incidences are based on proteinuria (albuminuria) this finding needs scrutiny.
Did you consider CKD as given based on a single finding of proteinuria already? If yes, can you say how many / what percentage of individuals had only a single increase in proteinuria and normalized again thereafter? The finding of "persistent" proteinuria is of relevance in this context as a single finding might be prone to chance or other intercurrent disease or condition but may not resemble CKD.

Response: We are grateful to the Reviewer for suggesting presenting further information about repeated measures of proteinuria. We have added further information to the results, including an additional sensitivity analysis, as summarised below

Results: *"Of the 5,581 participants who developed proteinuria during follow-up period, 3768 participants had at least one additional follow-up visit of whom 83.9% did not have proteinuria at the subsequent visit. For all definitions of persistent CKD (defined as meeting eGFR or proteinuria criteria for CKD at two consecutive visits), significantly increased risk was found for CAC <0-100 and CAC 101-300, compared with zero CAC, whereas non-significant increase in the risk was observed in CAC >300, albeit with a significant trend (P for trend = 0.003,* ***eTable 3****)"*

That said, we agree and acknowledge that our findings warrant confirmation by further studies with

UACR measurements. In order to clarify this point, we have added this point in the **Table 2** and in the **Results** section.

Footnote of the Table 2: *"proteinuria of 1+ grade refers to "30-<100 mg" of protein per dL. Proteinuria was defined as grade ≥1+ one or more times during follow-up period."*

Please also correct the proteinuria categories in table 2 according to values given in the text (chapter Measurements, e.g. page 33, line 59 where 1+ correlates with 30 mg/dL; is 1+ = 30-100 mg/dL?).

Response: We appreciate the Reviewer's suggestion. Proteinuria of 1+ refers to "30-<100 mg" of protein per dL. We have clarified this in the table foot note (see the response above). The left column of **Table 2** indicates the CAC score category. To differentiate the CAC score category as exposure from endpoint (eGFR or proteinuria), we have revised **Table 2**.

Table 2. Development of chronic kidney disease (CKD) and proteinuria by coronary artery calcification (CAC) score category (n = 113,171)

CAC score categories	Person-years (PY)	Incident cases	Incidence rate (per 10^3 PY)	Age-sex adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)	
					Model 1	Model 2
CKD eGFR<60 [b] ***as the outcome***						
0	474,782	375	0.79	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	49,791	135	2.71	1.54 (1.25-1.90)	1.31 (1.05-1.62)	1.27 (1.02-1.58)
101 to 300	5,759	29	5.04	1.67 (1.12-2.51)	1.41 (0.95-2.11)	1.42 (0.95-2.12)
>300	2,069	22	10.63	2.03 (1.27-3.24)	1.86 (1.16-3.00)	1.83 (1.14-2.95)
P for trend				<0.001	0.001	0.002
Per 100 increase in CAC score				1.06 (1.01-1.10)	1.02 (0.98-1.07)	1.03 (0.98-1.07)
Proteinuria of ≥1 + grade as the outcome						

0	463,073	4,831	10.43	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	48,441	613	12.65	1.30 (1.19-1.42)	1.11 (1.02-1.21)	1.07 (0.98-1.17)
101 to 300	5,599	92	16.43	1.73 (1.40-2.13)	1.32 (1.07-1.64)	1.26 (1.02-1.56)
>300	2,020	45	22.27	2.39 (1.77-3.23)	1.57 (1.16-2.12)	1.53 (1.13-2.07)
P for trend				<0.001	<0.001	0.001
Per 100 increase in CAC score				1.09 (1.07-1.12)	1.05 (1.02-1.08)	1.05 (1.02-1.09)
Either eGFR <60[b] ***or proteinuria as the outcome***						
0	462,319	5,143	11.12	1.00 (reference)	1.00 (reference)	1.00 (reference)
<0 to 100	48,173	726	15.07	1.33 (1.23-1.44)	1.15 (1.05-1.25)	1.11 (1.02-1.20)
101 to 300	5,538	114	20.59	1.77 (1.46-2.14)	1.37 (1.13-1.66)	1.31 (1.08-1.59)
>300	1,974	61	30.90	2.56 (1.98-3.32)	1.71 (1.32-2.22)	1.67 (1.29-2.17)

P for trend	<0.001	<0.001	<0.001
Per 100 increase in CAC score	1.09 (1.07-1.11)	1.06 (1.03-1.08)	1.06 (1.03-1.08)

[a] Estimated from Cox proportional hazard models. Multivariable model 1 was adjusted for age, sex, center, year of screening examination, smoking status, alcohol consumption, regular exercise, body mass index, education level, history of diabetes, history of hypertension, medication for dyslipidemia, and eGFR (for CKD); model 2: model 1 plus adjustment for systolic blood pressure, total cholesterol, HDL-cholesterol, triglyceride, glucose, and HOMA-IR.

[b] ml/min/1.73 m^2

Proteinuria of 1+ grade refers to "30-<100 mg" of protein per dL. Proteinuria was defined as grade ≥1+ one or more times during follow-up period.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; PY, person-years