Fasting ketonuria is inversely associated with coronary artery calcification in non-diabetic individuals

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Abstract

Background and Aims: Increased levels of ketone bodies, an alternative fuel when glucose availability is low, may exert beneficial effects on cardiovascular disease (CVD) risk factors. Whether increased ketone bodies are associated with coronary artery calcium (CAC), a recognized and strong cardiovascular risk factor, remains unknown. We investigated the association of fasting ketonuria with CAC and its progression.

Methods: Cross-sectional and longitudinal studies were conducted in adults without diabetes or CVD. Subjects underwent routine health examinations including cardiac computed tomography estimations of CAC scores. Logistic regression models were performed to compute the odds ratios (ORs), 95% confidence intervals (CIs), for prevalent CAC scores >0 according to fasting ketonuria categories (0, 1, and ≥2). Linear mixed models with random intercepts and random slopes were used to estimate CAC progression.

Results: Of 144,346 subjects, 12.3% had CAC scores >0 at baseline. Overall, higher fasting ketonuria was associated with decreased prevalence of coronary calcification than no ketonuria. Multivariable-adjusted ORs (95% CIs) for prevalent CAC by comparing ketonuria categories 1 and ≥ 2 with no ketonuria, were 0.94 (0.84–1.06) and 0.82 (0.71–0.95), respectively. The associations did not differ according to clinically relevant subgroups. Ketonuria was associated with lower CAC progression over time; the multivariable adjusted ratio of progression rates comparing ketonuria ≥ 2 versus no ketonuria was 0.976 (0.965–0.995).

Conclusions: We found an inverse association between fasting ketonuria and subclinical coronary atherosclerosis, in both prevalence and progression. The potentially protective role of increased ketone body formation in CVD requires further investigation.

Keywords: ketosis, ketone bodies, coronary artery calcium, coronary artery disease, atherosclerosis

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of death with an estimated 18.6 million deaths in 2019, and a predicted global increase of 18% by 2030.[1, 2] Though medications such as statins have markedly improved cardiovascular outcomes, patients who achieve the recommended low-density lipoprotein cholesterol (LDL-C) levels through intense statin therapy still have a significant residual CVD risk,[3, 4] with coronary artery calcium (CAC) as an important predictor of residual risk.[5] Furthermore, 20% of individuals with CVD have no established conventional risk factors.[6] Thus, it is important to assess new and novel risk factors for CVD, as it may be possible to treat these new risk factors and further lower the CVD risk.

Recently, both experimental and clinical studies have suggested the protective role of ketone bodies in CVD.[7] Ketone bodies are synthesized in the liver mainly through fatty acid oxidation and undergo oxidation for energy metabolism in the extrahepatic tissues during physiological states such as limited carbohydrate intake, strenuous exercise, and prolonged fasting.[8] Circulating ketone body concentrations can increase from < 0.3 mM during normal state to 1–3 mM after fasting, prolonged exercise,[9] or nutritional ketosis[10] in healthy adults. This is very different from the pathologic states such as diabetic ketoacidosis, in which ketone concentrations can increase to over 20 mM.[9] The metabolism and signaling roles and the epigenetic effects of ketone bodies at low to medium concentrations[11] have a beneficial effect on the vascular endothelium,[12] in protecting against inflammation and injury,[9] and in improving metabolic and inflammatory markers such as lipid profiles, insulin levels, hemoglobin A1c, fasting glucose, and high-sensitivity C-reactive protein (hsCRP).[13]

Ketonuria is an easily measured and relatively cost-effective indicator of ketosis that is often used as a common measure of adherence to the ketogenic diet.[14] Urinary ketone levels correlate well with quantitative serum ketone levels,[15] and urinary ketone testing is an

essential tool for monitoring patients, especially type 1 diabetic patients on insulin.[16] Recently, fasting ketonuria has been associated with decreased prevalence of obesity and metabolic syndrome[17] and with a lower risk of incident diabetes,[18] all of which may have a preventive effect against CVD. However, the clinical significance of fasting ketonuria in assessing coronary atherosclerosis remains unknown. CAC scores (CACS) obtained through computed tomography (CT) are useful for identifying subclinical coronary atherosclerosis[19] and for refining the estimated risk of prospective cardiovascular events.[20, 21] Therefore, our aim was to analyse the association between fasting ketonuria and subclinical coronary atherosclerosis assessed through CACS in a large sample of nondiabetic healthy adults who underwent routine health screening examinations. In this study, we investigated the association between fasting ketonuria and CAC using a cross sectional analysis, and the association between fasting ketonuria and CAC progression in a longitudinal analysis.

2. Patients and Methods

2.1. Study subjects

Study subjects belonged to the Kangbuk Samsung Health Study, which comprises a cohort of Koreans aged ≥ 18 years who receive comprehensive health examinations at one of the Kangbuk Samsung Hospital Total Healthcare Centres in either Seoul or Suwon, South Korea, on an annual or biennial basis.[22, 23] We included a subsample of the subjects who underwent a cardiac CT, allowing for CACS calculations, during their health examinations between 2011 and 2019. If a participant visited more than once with CACS measures, the first visit was chosen for the cross-sectional study (N = 164,048).

A total of 19,702 subjects were excluded due to (***Figure 1***): missing data on urinary ketone or body mass index (BMI) (n = 4,183), diabetes (defined as having a fasting serum glucose ≥ 126 mg/dL [7.0 mmol/L], glycated hemoglobin ≥ 6.5% [48 mmol/mol], or self-reported

insulin or medication for diabetes) (n = 9,884), malignancy history (n = 4,653), and self-report of previous CVD history (n = 2,179). Since some subjects had more than one exclusion criterion, 144,346 non-diabetic participants without clinically evident CVD were included for the analysis. For the longitudinal analysis, we analysed a subset of study subjects who had a baseline and at least one follow-up cardiac CT (n = 40,695). This study complied with the Declaration of Helsinki, and was granted approval by the Institutional Review Board of the Kangbuk Samsung Hospital (IRB no. KBSMC 2021-01-039), which waived the need for informed consent because we analysed de-identified retrospective data obtained from routine health screenings.

2.2. Measurements

Data on physical measurements, and serum biochemical measurements were retrieved from the routine health screening programs. Information on the subjects' demographics, lifestyle behaviours, and medical history was obtained using standardized, self-report questionnaires.[22, 23] Current alcohol use was determined based on the frequency of alcohol consumption per week and the amount consumed per occasion. Physical activity levels were estimated using the Korean International Physical Activity Questionnaire-Short Form, which was previously validated.[24] Health-enhancing physical activity (HEPA) was assessed as physical activity that met the following criteria: (1) vigorous activity ≥ 3 days/week, for a total of ≥ 1,500 metabolic equivalent -min/week or (2) walking or performing moderate/vigorous intensity activities for 7 days, for a total of ≥ 3,000 metabolic equivalent -min/week.[24] Information on dietary patterns was collected through a 103-item food frequency questionnaire (FFQ). Participants were first asked whether their diet had changed markedly during the past year compared with a previously maintained diet; if they answered "No", they proceeded with the FFQ and if they answered "Yes," they were instructed to answer

according to their usual diet.

Nurses were trained to measure the blood pressure (BP), height, weight, and waist circumference of the study subjects. Hypertension was determined based on systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current use of any antihypertensive medication.

Blood and urine samples were obtained after a minimum of 10 hours of fasting. The blood sample measurements included those of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, glucose, and hsCRP. Insulin resistance was based on the homeostatic model assessment of insulin resistance (HOMA-IR): fasting serum insulin (mU/mL) × fasting serum glucose (mmol/L) / 22.5. For semi-quantitative measurement of urine ketone levels, urine dipstick was used (URiSCAN urine test strips; YD Diagnostics, Yongin-si, Republic of Korea). This urine dipstick-based ketonuria and serum β-hydroxybutyrate (βHB) levels had been compared previously, and serum βHB levels gradually increased with increasing ketonuria levels (p for trend <0.001).[18] The levels of urine ketone bodies were reported as absent, trace (50 mg/L [0.49 mmol/L]), 1+ (100 mg/L [0.98 mmol/L]), 2+ (500 mg/L [4.9 mmol/L]), and 3+ (1,000 mg/L [9.8 mmol/L]). For analysis of fasting ketonuria as the key exposure, results were categorized as 1) absent or trace, 2) 1+, and 3) ≥ 2+.

The abdominal ultrasound findings of fatty liver were interpreted by an experienced radiologist using standard criteria, which included diffuse increase in fine echoes of the liver relative to that observed in the spleen or kidney, deep beam attenuation, and brightening of the vasculature.[25]

2.3. CAC measurement

CAC was detected using a LightSpeed VCT XTe-64 slice multidetector computed tomography scanner (GE Healthcare, Tokyo, Japan) with the same standard scanning

protocol[22] of 400-ms rotation time, 2.5-mm thickness, 120-kV voltage, and 124-mAS (310 mA x 0.4 s) tube current under electrocardiogram-gated dose modulation in both the Seoul and Suwon centres. The calcium score was analysed using semi-automatic methodology with GE Smartscore software (GE Healthcare), and confirmed by experienced technicians and radiologists. CACS were calculated using the method proposed by Agatston et al.[26] The inter-observer and intra-observer reliabilities for CACS were excellent (intraclass correlation coefficient = 0.99), as previously reported.[22]

2.4. Statistical analysis

The study subjects' characteristics were examined through descriptive statistics, according to the key exposure ketonuria categories (0, 1, and ≥2). For the association between CACS and ketonuria categories, we performed logistic regression analyses to compute the odds ratios (ORs) with 95% confidence intervals (CIs) for prevalent CACS > 0. We also performed a sensitivity analysis with CACS ≥ 10 as the outcome. Additionally, we presumed that CACS were distributed log-normally, with left-censored data at 0 Agatston units (i.e., non-detectable scores). Hence, as secondary analyses evaluating the association between ketonuria categories and CACS as a continuous variable with left censoring, Tobit regression analysis was performed with natural log (CACS + 1) as the outcome, using Huber–White estimation of standard errors.[27, 28] We used Tobit models to compute the ratios and 95% CIs of CACS + 1, and compared ketonuria categories with the no ketonuria category.

We used two models for adjustment of covariates: Model 1 was adjusted for the subjects' age and sex; Model 2 was additionally adjusted for the centre (Seoul or Suwon), year of the health screening exam, smoking (never, past, current, or unknown), average alcohol consumption (0, <20, ≥20 g/day, or unknown), highest level of education achieved (≤high school graduate, college or university graduate, ≥graduate school, or unknown), total energy

intake (quintiles, or unknown), medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C. Confounding variables were selected according to the following criteria: 1) causally associated with the outcome (CACS) and 2) non-causally or causally associated with the exposure (ketonuria) and 3) is not an intermediate variable in the pathway between the exposure (ketonuria) and outcome (CACS).[29]

Predefined subgroup analyses were conducted for age in years (<50 vs. ≥50), sex (male vs. female), current smoking (non-current smokers vs. current smokers), average alcohol consumption (<20 vs. ≥20 g/day), performance of HEPA (no vs. yes), BMI (<18 kg/m^2, 18.5–22.9 kg/m^2, 23–24.9 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2, in accordance with Asian-specific BMI criteria[30]), glucose (<100 mg/dL vs. ≥100 mg/dL), HOMA-IR (<2.5 vs. ≥2.5), hsCRP (<1.0 vs. ≥1.0 mg/L), and fatty liver (no vs. yes). We examined the interactions between fasting ketonuria categories and each subgroup by performing likelihood ratio tests and comparing models with and without multiplicative interaction terms.

We also analysed the prospective association between fasting ketonuria and CAC progression. We performed linear mixed models with random intercept and random slopes[31] for estimating progression of CACS over time, with adjustment for potential confounders. We transformed CACS as natural log(CACS+1) for the outcome, because CACS were right-skewed. The annual CAC progression rates with 95% CI were calculated, with 2 models for adjustment of covariates: Model 1 was adjusted for age and sex, and Model 2 was further adjusted for centre, year of screening exam, smoking, alcohol intake, educational level, total energy intake, medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C. We also performed a sensitivity analysis by setting a higher threshold for CAC and calculated the hazard ratios for incident CACS ≥10 among participants with CACS = 0 at baseline.

Statistical analyses were performed using STATA version 16.0 (StataCorp LP, College Station, TX, USA). Two-sided *p*-values < 0.05 were determined as significant.

3. Results

3.1. Characteristics of study participants

Table 1 shows the characteristics of the 144,346 participants without known CVD according to the fasting ketonuria category. The presence of fasting ketonuria was positively associated with HEPA and HDL-C, and was inversely associated with male sex, alcohol intake, current smoking, hypertension, obesity, BP, glucose, LDL-C, triglycerides, HOMA-IR, and total energy intake. Participants in the ketonuria category ≥2 showed lower total energy intake, and slightly lower carbohydrate and slightly higher fat intake than participants in the no ketonuria category. Although lipid-lowering agent use appeared to be higher in the no ketonuria category than categories 1 and ≥2, there was no difference after adjustment for age, sex, and BMI (p for trend = 0.333, **Supplementary Table 1**).

3.2. Association between fasting ketonuria and CAC

Table 2 shows the prevalence of CAC based on the fasting ketonuria category. Of the 144,346 participants, 17,762 (12.3%) had detectable CACS > 0. Overall, a higher fasting ketonuria level was associated with lower prevalence of coronary calcification than no ketonuria. The age- and sex-adjusted ORs (95% CIs) for prevalent CACS comparing fasting ketonuria categories 1 and ≥ 2 with no ketonuria (reference) were 0.91 (0.82–1.02) and 0.77 (0.67–0.88), respectively. After adjustment for age, sex, year and centre of screening examination, smoking, alcohol consumption, education, total energy intake, medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C, the multivariable-adjusted ORs (95% CIs) for prevalent CACS comparing fasting ketonuria categories 1 and ≥ 2 to no ketonuria were 0.94 (0.84–1.06) and 0.82 (0.71–0.95), respectively. The observed association between ketonuria categories and CACS was similar when analyses were performed with

CACS ≥ 10 as the outcome, with a multivariable-adjusted OR (95% CI) of 0.74 (0.62–0.88) for ketonuria ≥ 2 vs. no ketonuria (**Supplementary Table 2**).

Similarly, in the Tobit regression analysis (**Table 3**), the multivariable-adjusted CACS ratios which compared fasting ketonuria categories 1 and ≥ 2 with the no ketonuria category were 0.91 (0.72–1.15) and 0.66 (0.49–0.88), respectively.

The associations observed above did not differ among clinically relevant subgroups in terms of age, sex, smoking, average alcohol consumption, performance of HEPA, BMI, glucose, HOMA-IR, hsCRP, and presence of fatty liver (**Supplementary Table 3**).

Finally, we evaluated prospective association between fasting ketonuria and progression of CACS over time among those with a follow-up CAC CT (n = 40,695).
The median duration of follow-up was 4.0 years (interquartile range 2.6-5.7, maximum 8.7). The annual rates of CAC progression for no ketonuria, ketonuria category 1, and category ≥ 2 were 8.7%, 7.9%, and 6.2%, respectively (**Table 4**). The multivariable adjusted ratios (95% CI) of annual progression rates comparing fasting ketonuria categories 1 and ≥ 2 vs. no ketonuria were 0.994 (0.980–1.009) and 0.976 (0.965–0.995), respectively. For incident CACS ≥10 as the outcome, among participants with CACS = 0 at baseline, the multivariable-adjusted hazard ratios (95% CI) in ketonuria categories 1 and ≥2 vs. no ketonuria were 1.11 (0.83–1.49) and 0.80 (0.53–1.18), respectively (**Supplementary Table 4**).

4. Discussion

Our study is the first to show an inverse association between fasting ketonuria and CAC using a large sample of non-diabetic Korean adults. Adults with higher fasting ketonuria levels showed a lower prevalence of CAC compared to those without ketonuria. This association remained even after adjusting for predictors of coronary atherosclerosis (age, current smoking, alcohol consumption, hypertension, medication for hyperlipidaemia, SBP,

and LDL-C) and did not differ in the subgroup analyses, including in the presence or absence of fatty liver. Among participants with a follow-up CAC test, ketonuria of ≥ 2 was also associated with lower CAC progression over time.

In our study, subjects with fasting ketonuria showed a lower prevalence of hypertension and more favourable lipid profiles than those without ketonuria, which are possibly related to the healthier lifestyle behaviours observed in this group such as higher physical activity, lower alcohol consumption, and less smoking. Likewise, low-carbohydrate ketogenic diets are associated with weight loss, improved lipid profiles and glucose levels,[12, 32] as well as the improvement of non-alcoholic fatty liver disease.[33] Though this association is thought to be attributable to ketosis, it may also be related to reduced energy intake in participants consuming low-carbohydrate ketogenic diets.[34] In our study, participants with fasting ketonuria also had lower total energy intake than those without ketonuria. However, adjusting for lifestyle behaviours, total energy intake, hypertension, medication for hyperlipidaemia, SBP, and LDL-C did not completely attenuate the association between fasting ketonuria and CACS.

Nonetheless, clearly favourable metabolic profiles in individuals with fasting ketonuria may be accountable for the reduction in the prevalence of CAC and its progression. Previous studies have shown that sporadic or fasting ketonuria is associated with favourable metabolic profiles[17] and a lower risk of incident diabetes.[18] A previous study that confirmed the presence of nutritional ketosis through blood measurements found that inflammatory responses measured through hsCRP and white blood cell count, triglycerides, small dense LDL particles, and the 10-year risk of atherosclerotic CVD decreased with ketogenic diets.[35] However, studies analysing the effect of ketogenic diets on carotid atherosclerosis in diabetic patients showed that there were no differences between those with induced nutritional ketosis and those under usual care.[35, 36] Indeed, individuals with manifest diabetes or features of the

metabolic syndrome may be resistant to ketonuria or less likely to benefit from ketosis.[37] In previous studies of individuals either practicing Ramadan fasting[38] or following a ketogenic diet,[39] obese subjects did not show ketosis, while non-obese subjects showed elevated urine ketone levels. However, in our study the association between fasting ketonuria and CAC did not differ in subgroup analysis according to BMI, glucose, HOMA-IR, and presence of fatty liver. Interestingly, the inverse association between ketonuria and CAC was not observed in the underweight group (<18.5 kg/m^2); however, the inconclusive result for the underweight group can be explained by the small number included in this category, which may have been insufficient to establish a relationship and may have led to imprecise estimates.

Fasting ketonuria was present in 5.7% of our study population, showing that this condition is not an uncommon phenomenon in non-diabetic individuals. In previous studies including relatively healthy populations, fasting ketonuria was present in 2.2%[18] and 8.8%[17] of the study population. Non-diabetic individuals with fasting ketonuria may have a greater capacity for ketogenesis and oxidation of fat than those without fasting ketonuria under certain conditions such as fasting or low-carbohydrate ketogenic diets. The beneficial effects of ketogenic diets are attributed to the metabolic shift to ketones over glucose as an energy source,[13] and low-carbohydrate ketogenic diets have been explored for their associations with favourable metabolic profiles, weight loss, and reduced cardiovascular risk, but have not always shown consistent results.[34] The ability to regulate ketogenesis and an individual's metabolic or genetic background as well as the difference in the composition of ketogenic diets may underlie the discrepancies in previous studies.[40] The rate of hepatic ketogenesis is proportional to total fat oxidation,[9] possibly indicating that ketonuria might be reflective of high fat oxidation ability. The circulating ketone body levels vary across healthy adult populations even after controlling for age and fasting hours;[16] hence, future studies including markers of ketosis and genetic variability may help clarify the metabolic and cardiovascular

effects of ketosis. In addition, the 10 hours of fasting in our study participants may have been a relatively short time window for inducing ketosis, since most intermittent fasting regimens recommend longer periods of fasting, such as 16 hours of fasting between 8 hours of eating.[41, 42] Studies with longer periods of fasting may provide more insight into the association between fasting ketonuria and CAC.

The mechanism responsible for the association between fasting ketonuria and CAC in relatively healthy adults without diabetes is unclear. Ketone bodies have a pleiotropic effect as signaling molecules and epigenetic modifiers, as well as metabolic intermediates.[12] The ketone body β-hydroxybutyrate inhibits histone deacetylase activity, which is known to extend lifespan in model organisms.[11] While high ketone body levels in patients with diabetic ketoacidosis are detrimental to the vascular system, recent studies have shown that ketone bodies at low levels may have beneficial effects on the endothelium through modulation of the inflammatory status,[9] senescence, and metabolism of the endothelial cells.[12] Inflammation is a well-known atherogenic factor, and the anti-inflammatory effect of low ketone body concentrations[9, 12] may be beneficial for coronary atherosclerosis.[10] Nutritional ketosis through restriction of carbohydrate intake reduces insulin levels,[13] and insulin at low levels is beneficial for the vasculature through its association with nitric oxide production, vasodilation, decreased monocyte adhesion, and reduced inflammation and oxidative stress.[43] Nevertheless, further studies controlling for the method of inducing ketosis are warranted to explain the associations found in our study.

4.1. Clinical implications

Several methods such as low-carbohydrate ketogenic diets and intermittent fasting are available for inducing ketosis. Exercise may be recommended as an adjunct for improving coronary vascular health, as it facilitates β-oxidation and ketogenesis through depletion of

glycogen stores and by increasing the energy demand, and may enhance the signaling induced by ketosis.[10] Ketosis can also be induced by ingestion of exogenous ketones in the form of ketone salts or ketone esters, or by ingesting precursors such as medium-chain triglycerides or 1,3-butanediol.[7] Nevertheless, low-carbohydrate diets that are high in fat may exacerbate or induce the occurrence of hypercholesterolemia in patients with genetic predisposition to hypercholesterolemia, and precautionary measures such as monitoring of lipid levels and ketosis may be required when recommending ketogenic diets.[44] Although LDL-C appeared to decrease with increasing ketonuria category in our study participants, after adjustment for age, sex, and BMI, LDL-C was lowest in the no ketonuria category. Furthermore, it is unclear whether any predisposing factors for ketonuria played a role in our study population, as information on the reason for ketonuria, such as genetic predisposition, longer fasting duration, recent dietary characteristics, or adherence to intermittent fasting, was not available. Nonetheless, our results indicate that ketosis may have an underestimated impact on the primary prevention of coronary heart disease and progression of coronary atherosclerosis. Further studies are needed to confirm whether these methods for inducing ketosis are beneficial for coronary atherosclerosis.

4.2. Limitations

Despite the strengths of our study, including the large population of relatively healthy individuals without diabetes, laboratory measurements, and lifestyle factors, some limitations should be noted. First, semi-quantitative urine tests were used to assess fasting ketonuria as a surrogate marker of ketosis. That said, urinary ketone levels correlate well with serum ketone levels[15] and remain an essential tool for monitoring patients.[16] Second, because this was an observational study, the reasons underlying the differences in fasting ketonuria between the study subjects remain unclear. Future studies controlling for methods that induce ketosis may

help clarify the association between ketosis and coronary atherosclerosis. Third, information on fasting time, recent dietary habits and intermittent fasting, which may affect ketonuria levels, was not available. Dietary information was collected through self-administered FFQs, which reflect usual food intake throughout the previous year, and may not reflect recent diet compositions.[45] The FFQ is also limited in assessing macronutrient composition and may underestimate fat and cholesterol intake compared with dietary records, because it does not include seasonings and oils, which are used in pre-seasoned dishes typical in South Korean diets.[45] Fourth, information on ketonuria was collected once at baseline; thus, the changing status of ketonuria was not incorporated into the analysis. Finally, our study included relatively healthy, young, middle-aged Koreans, thus limiting the generalizability of our results to populations of other ethnicities or with other comorbidities.

4.3. Conclusions

Our study showed that fasting ketonuria, especially at higher levels, was associated with a decreased CAC prevalence and lower CAC progression in non-diabetic individuals. Ketosis may have a beneficial effect on coronary atherosclerosis, but further studies are warranted to confirm this association.

Conflict of interest: None declared.

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Figure legends

Figure 1 Study participants selection process.

Table 1 Baseline characteristics by fasting ketonuria category

Characteristics	**Overall**	**Fasting ketonuria category**			***p* for trend**
		0	**1**	**≥2**	
Number of participants	144,346	136,159	4,486	3,701	
Age (years)	41.3 (8.4)	41.3 (8.4)	40.5 (8.9)	39.4 (8.4)	<0.001
Men (%)	75.8	76.6	65.1	61.2	<0.001
Seoul centre (%)	48.8	48.6	56.3	49.0	<0.001
Alcohol intake[a] (%)	44.4	44.8	39.3	36.5	<0.001
Current smoker (%)	22.1	22.5	16.8	13.0	<0.001
HEPA (%)	19.0	16.4	16.2	18.5	<0.001
High education level[b] (%)	83.4	83.4	83.9	83.9	0.231
Hypertension (%)	14.7	14.9	12.3	10.5	<0.001
Family history of CVD (%)	12.0	12.0	12.9	12.0	0.357
Lipid lowering agent (%)	3.5	3.6	2.6	2.8	<0.001
Fatty liver (%)	38.9	39.7	27.4	24.8	<0.001
BMI category					

<18.5 kg/m^2	2.3	2.2	3.7	5.1	<0.001
18.5-22.9 kg/m^2	32.8	32.2	42.8	45.6	<0.001
23-24.9 kg/m^2	26.1	26.2	24.3	22.8	<0.001
25-29.9 kg/m^2	33.7	34.2	25.2	22.7	<0.001
≥30 kg/m^2	5.1	5.2	3.9	3.9	<0.001
BMI (kg/m^2)	24.3 (3.3)	24.4 (3.3)	23.5 (3.3)	23.3 (3.4)	<0.001
SBP (mmHg)	112.4 (12.4)	112.5 (12.4)	111 (12.6)	110 (12.7)	<0.001
DBP (mmHg)	72.7 (9.8)	72.8 (9.8)	71 (9.6)	69.8 (9.5)	<0.001
Glucose (mg/dL)	95.6 (8.4)	95.9 (8.2)	90.9 (8.5)	87.1 (10.2)	<0.001
Total cholesterol (mg/dL)	199 (34.1)	199.1 (34)	198.8 (35.3)	197 (36)	0.001
LDL-C (mg/dL)	130.1 (32.1)	130.2 (31.9)	129.2 (34.2)	127.7 (34.6)	<0.001
HDL-C (mg/dL)	64 (29.4)	63.8 (29.6)	67.9 (27.2)	68.4 (25.9)	<0.001
Triglycerides (mg/dL)	109.0 (76.0–158.0)	112.0 (79.0–162.0)	74.0 (56.0–104.0)	66.0 (52.0–89.0)	<0.001
hsCRP (mg/L)	0.5 (0.3–1.0)	0.5 (0.3–1.0)	0.5 (0.3–1.1)	0.5 (0.3–1.2)	0.003
HOMA-IR	1.45 (0.97–2.15)	1.49 (1.00–2.19)	0.93 (0.60–1.44)	0.78 (0.46–1.24)	<0.001

Total energy intake (kcal/d)[c]	1430 (1070–1826)	1432 (1074–1826)	1405 (1028–1825)	1363 (981–1808)	<0.001
Carbohydrate proportion (%)	68.1 (61.3–73.9)	68.2 (61.4–74.0)	67.2 (60.2–73.0)	67.1 (59.4–72.9)	<0.001
Fat proportion (%)	18.2 (13.8–23.3)	18.1 (13.7–23.3)	18.8 (14.3–24.1)	19.0 (14.7–24.9)	<0.001
Protein proportion (%)	13.6 (12.0–15.6)	13.6 (12.0–15.6)	13.8 (12.0–15.9)	13.8 (12.1–15.9)	<0.001
Carbohydrate <50 g/day (%)	5.5	5.4	6.5	7.2	0.016
CACS category					
0 AU	87.7	87.5	89.9	92.8	<0.001
1-100 AU	10.2	10.4	8.1	6.1	<0.001
>100 AU	2.1	2.1	2.0	1.2	<0.001

Data are presented as mean (standard deviation), median (interquartile range), or percentages.

Abbreviations: HEPA, health-enhancing physical activity; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; CACS, coronary artery calcium score; AU, Agatston unit.

[a] ≥20 g of ethanol per day.

[b] ≥College graduate.

[c] Among 87,482 participants with plausible estimated energy intake (within three standard deviations of the log-transformed mean energy intake).

Table 2 Odds ratios[a] (95% CIs) for coronary artery calcification by fasting ketonuria category in 144,346 health checkup examinees at Kangbuk Samsung Hospital between 2011 and 2019

	Fasting ketonuria category			***p* for trend**
	0	**1**	**≥2**	
Number	136,159	4,486	3,701	
Cases (N) of CACS >0	17,041	453	268	
Age- and sex-adjusted prevalence[b] (95% CIs)	12.4 (12.2–12.5)	11.6 (10.7–12.5)	10.2 (9.1–11.2)	
Adjusted odds ratios [a] (95% CIs)				
Age- and sex-adjusted	1.00 (reference)	0.91 (0.82–1.02)	0.77 (0.67–0.88)	<0.001
Multivariable-adjusted	1.00 (reference)	0.94 (0.84–1.06)	0.82 (0.71–0.95)	0.004

Abbreviations: CACS, coronary artery calcium scores; CI, confidence interval.

[a] Estimated from binomial logistic regression models used with prevalent CACS >0 as the outcome

The multivariable model was adjusted for age, sex, centre, year of screening exam, smoking status, alcohol intake, educational level, total energy intake, medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C.

[b] per 100 persons.

Table 3 Coronary artery calcium score (CACS) ratios[a] (95% CI) by fasting ketonuria category of 144,346 health checkup examinees at Kangbuk Samsung Hospital between 2011 and 2019

	Fasting ketonuria category			***p* for trend**
	0	**1**	**≥2**	
Number	22,052	22,385	21,595	
Adjusted CACS ratios[a] (95% CIs)				
Age- and sex-adjusted	1.00 (reference)	0.85 (0.66–1.08)	0.56 (0.42–0.76)	<0.001
Multivariable-adjusted	1.00 (reference)	0.91 (0.72–1.15)	0.66 (0.49–0.88)	0.005

Abbreviations: CI, confidence interval.

[a] Estimated from robust Tobit regression models performed with natural log(CACS+1) as the outcome.

The multivariable model was adjusted for age, sex, centre, year of screening exam, smoking status, alcohol intake, educational level, total energy intake, medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C.

Table 4 Ratio (95% CI) of annual progression rates of coronary artery calcium score by fasting ketonuria category at baseline (n = 40,695)

Ratio of annual progression rates[a]	**Fasting ketonuria category**		
	0	**1**	**≥2**
Number	38,558	1,201	936
Annual rate of CAC progression	1.087 (1.085–1.090)	1.079 (1.066–1.092)	1.062 (1.049–1.076)
Ratio of annual progression rates[a]			
Model 1	1.0 (reference)	0.992 (0.980–1.004)	0.976 (0.964–0.988)
Model 2	1.0 (reference)	0.994 (0.980–1.009)	0.976 (0.965–0.995)

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, centre, year of screening exam, smoking status, alcohol intake, educational level, total energy intake, medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C.

Abbreviations: CAC, coronary artery calcification; CI, confidence interval.

[a] Estimated from linear mixed models with random intercept and random slopes used with natural log(CAC+1) as the outcome and inverse probability weighting.