

Supplementary Material

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

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**Supplementary Table 1.** Estimated<sup>a</sup> mean values (95% CI) and adjusted<sup>a</sup> proportion (95% CI) of baseline characteristics by fasting ketonuria category

Characteristics	Fasting ketonuria category			<i>p</i> for trend
	0	1	≥2	
Total cholesterol (mg/dL)	198.9 (198.8-199.1)	200.8 (199.7-201.8)	199.9 (198.8-201.1)	0.003
LDL-C (mg/dL)	130.0 (129.8-130.1)	131.8 (130.9-132.7)	131.6 (130.6-132.6)	<0.001
HDL-C (mg/dL)	63.9 (63.8-64.1)	66.2 (65.3–67.0)	66.1 (65.1–67.0)	<0.001
Triglycerides (mg/dL)	132.6 (132.2-133.1)	97.7 (95.3–100.1)	91.0 (88.4–93.7)	<0.001
Lipid lowering agent (%)	3.6 (3.5-3.7)	2.9 (2.4-3.4)	3.6 (2.9-4.4)	0.333

CI, confidence interval; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein cholesterol

<sup>a</sup>Adjusted for age, sex and BMI

**Supplementary Table 2.** Odds ratios<sup>a</sup> (95% CIs) for CACS  $\geq 10$  by fasting ketonuria category in 144,346 health checkup examinees at Kangbuk Samsung Hospital between 2011 and 2019

	Fasting ketonuria category			<i>p</i> for trend
	0	1	$\geq 2$	
Number	136,159	4,486	3,701	
Cases (N) of CACS $\geq 10$	11,078	293	155	
Age- and sex-adjusted prevalence <sup>b</sup> (95% CIs)	8.0 (7.9–8.2)	7.3 (6.6–8.1)	6.0 (5.1–6.8)	
Adjusted odds ratios <sup>a</sup> (95% CIs)				
Age- and sex-adjusted	1.00 (reference)	0.89 (0.78–1.02)	0.68 (0.57–0.81)	<0.001
Multivariable-adjusted	1.00 (reference)	0.93 (0.81–1.06)	0.74 (0.62–0.88)	0.001

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

<sup>a</sup> Estimated from binomial logistic regression models used with prevalent CACS  $\geq 10$  as the outcome

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

<sup>b</sup> per 100 persons.

**Supplementary Table 3.** Coronary artery calcium score (CACS) ratios<sup>a</sup> (95% CI) by fasting ketonuria category in clinically relevant subgroups

Subgroup	Fasting ketonuria category			<i>p</i> for trend	<i>p</i> for interaction
	0	1	≥2		
<b>Age</b>					0.106
<50 years (N=125,028)	Reference	0.67 (0.49-0.90)	0.45 (0.31-0.63)	<0.001	
≥50 years (N=19,318)	Reference	1.01 (0.65-1.56)	0.76 (0.41-1.39)	0.481	
<b>Sex</b>					0.532
Women (N=34,896)	Reference	0.89 (0.51-1.55)	0.89 (0.48-1.65)	0.621	
Men (N=109,450)	Reference	0.91 (0.70-1.19)	0.60 (0.43-0.83)	0.003	
<b>Current smoking</b>					0.967
No (N=107,642)	Reference	0.92 (0.69-1.22)	0.63 (0.45-0.88)	0.008	
Yes (N=30,471)	Reference	0.93 (0.56-1.54)	0.69 (0.36-1.35)	0.294	
<b>Alcohol intake</b>					0.516
<20 g/day (N=102,123)	Reference	0.81 (0.60-1.09)	0.68 (0.48-0.96)	0.010	
≥20 g/day (N=34,727)	Reference	1.11 (0.70-1.76)	0.70 (0.39-1.27)	0.450	
<b>HEPA</b>					0.838

No (N=118,928)	Reference	0.87 (0.66-1.15)	0.66 (0.47-0.93)	0.011	
Yes (N=23,297)	Reference	1.03 (0.63-1.68)	0.65 (0.35-1.20)	0.255	
<b>BMI</b>					0.521
<18.5 kg/m <sup>2</sup> (N=3,337)	Reference	2.16 (0.44-10.74)	1.21 (0.21-6.94)	0.555	
18.5-22.9 kg/m <sup>2</sup> (N=47,399)	Reference	0.86 (0.57-1.30)	0.84 (0.52-1.35)	0.336	
23-24.9 kg/m <sup>2</sup> (N=37,656)	Reference	0.85 (0.54-1.32)	0.38 (0.20-0.69)	0.002	
25-29.9 kg/m <sup>2</sup> (N=48,581)	Reference	0.91 (0.60-1.39)	0.75 (0.45-1.24)	0.707	
≥30 kg/m <sup>2</sup> (N=7,373)	Reference	1.12 (0.39-3.18)	0.35 (0.09-1.37)	0.409	
<b>Glucose</b>					0.226
<100 mg/dL (N=103,735)	Reference	1.00 (0.77-1.30)	0.71 (0.52-0.98)	0.068	
≥100 mg/dL (N=40,610)	Reference	0.65 (0.38-1.11)	0.47 (0.23-0.97)	0.011	
<b>HOMA-IR</b>					0.554
<2.5 (N=118,849)	Reference	0.94 (0.73-1.21)	0.70 (0.51-0.94)	0.024	
≥2.5 (N=25,283)	Reference	0.79 (0.33-1.90)	0.39 (0.13-1.14)	0.095	
<b>hsCRP</b>					0.632
<1.0 mg/L (N=92,491)	Reference	1.05 (0.77-1.44)	0.78 (0.53-1.15)	0.370	

≥1.0 mg/L (N=34,364)	Reference	0.83 (0.53-1.30)	0.67 (0.39-1.14)	0.090	
<b>Fatty liver</b>					0.180
No (N=88,020)	Reference	0.88 (0.65-1.19)	0.78 (0.55-1.11)	0.115	
Yes (N=56,033)	Reference	0.99 (0.67-1.44)	0.44 (0.26-0.74)	0.007	

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<sup>a</sup> Estimated from robust Tobit regression models performed with natural log(CACS + 1) as the outcome. The multivariable model was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, educational level, total energy intake, medication for hyperlipidaemia, history of hypertension, SBP, and LDL-C.

Abbreviations: CI, confidence interval; HEPA, health-enhancing physical activity; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein

**Supplementary Table 4.** Hazard ratios<sup>a</sup> (95% CIs) for coronary artery calcium score (CACs)  $\geq 10$  by fasting ketonuria category among participants with CACS = 0 (n=33,774)

	Fasting ketonuria category			<i>p</i> for trend
	0	1	$\geq 2$	
Person-year	130004.7	4441.0	3644.7	
Incident CACS $\geq 10$	1411	46	25	
Incident density (/10 <sup>3</sup> )	10.9	10.4	6.9	
Multivariable adjusted hazard ratios <sup>a</sup> (95% CIs)	1.00 (reference)	1.11 (0.83-1.49)	0.80 (0.53-1.18)	0.259

Abbreviations: CI, confidence interval.

<sup>a</sup> Estimated from Cox proportional hazard models

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