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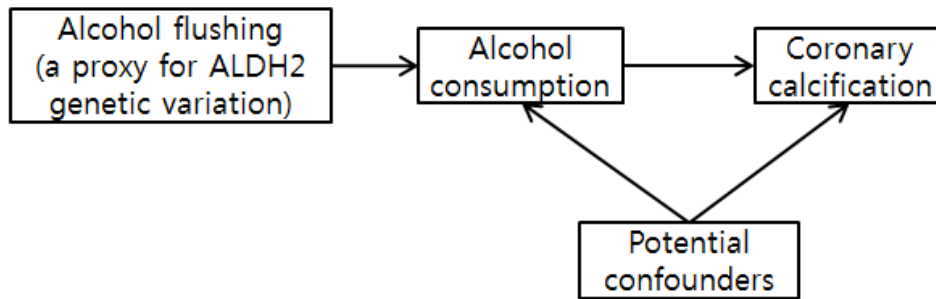
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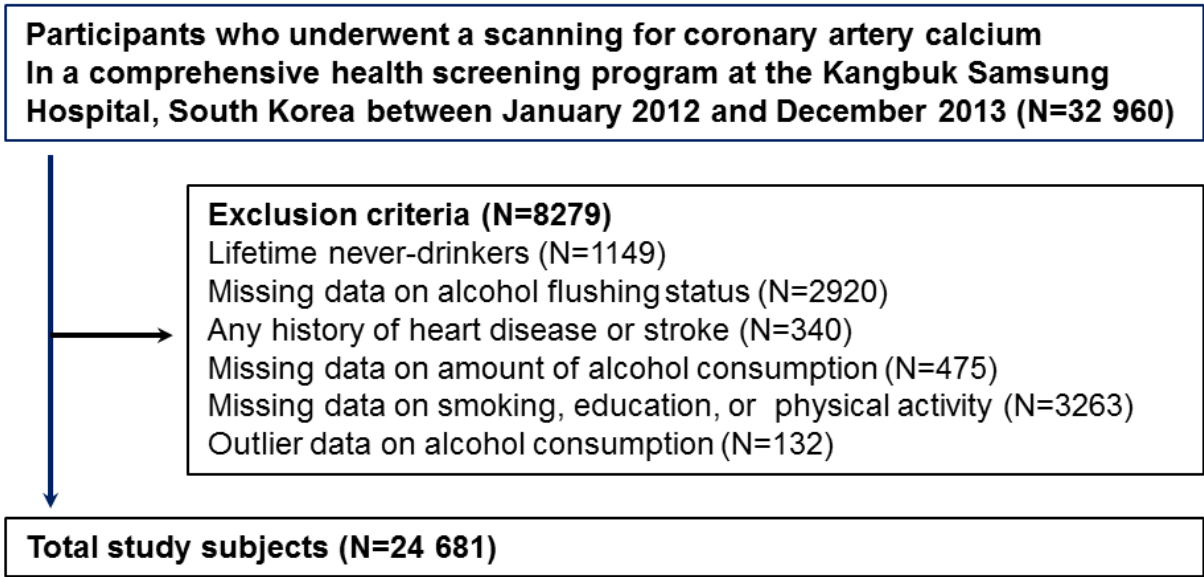
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## Supplementary materials



Supplementary Figure 1. Directed acyclic graph showing the framework of this study, in which alcohol flushing (a proxy for genetic variation in aldehyde dehydrogenase 2 [ALDH2]) was used as an instrumental variable.



Supplementary Figure 2. Flow diagram of how the study subjects were identified.

Supplementary Table 1. Relationship of age with alcohol flushing status and alcohol consumption.

Variables	Age (years)													
	Men							Women						
	Overall	<30	30–39	40–49	50–59	≥60	P-value	Overall	<30	30–39	40–49	50–59	≥60	P-value
Number	20 696	94	8244	9847	2161	350		3985	201	1539	1847	318	80	
Alcohol flushers	28.7	32.9	29.0	27.9	29.8	34.2	0.030	28.4	31.3	29.5	29.0	25.5	27.5	0.603
Alcohol consumption														
0 g/day	7.6	4.3	9.6	6.3	5.6	10.9	<0.001	22.8	4.5	28.3	19.6	23.3	36.3	<0.001
<8 g/day	39.5	37.2	42.9	37.7	34.5	42.3		66.1	72.1	59.3	71.5	65.1	58.8	
8–30 g/day	37.0	39.4	35.0	38.4	39.2	31.1		9.4	17.9	10.7	7.4	10.1	5.0	
≥30 g/day	15.9	19.2	12.5	17.6	20.7	15.7		1.8	5.5	1.7	1.5	1.6	0.0	

Unless otherwise indicated, data are presented as percentages.

Supplementary Table 2. Relationships between alcohol consumption and covariates among men and women.

	Men					Women				
	0 g/day (n=1578)	<8 g/day (n=8174)	8–30 g/day (n=7664)	≥30 g/day (n=3280)	P-value	0 g/day (n=910)	<8 g/day (n=2632)	8–30 g/day (n=373)	≥30 g/day (n=70)	P-value
Age (years) <sup>a</sup>	39.6 (7.1)	40.3(7.0)	41.0 (6.8)	42.0 (7.0)	<0.001	39.9 (7.5)	40.1 (7.4)	38.3 (7.9)	38.9 (9.4)	<0.001
Education <sup>b</sup>										
Elementary or less	0.3	0.2	0.2	0.2	<0.001	3.0	1.1	2.4	2.9	<0.001
Middle or high school	8.6	8.9	11.5	19.4		17.0	25.9	33.8	51.4	
College or over	91.1	90.9	88.3	80.4		80.0	73.0	63.8	45.7	
Monthly household income <sup>b</sup>					<0.001					<0.001
<4,000 USD	22.9	20.4	19.6	20.1		21.8	19.9	24.7	35.7	
4,000–5,999 USD	31.9	33.8	33.5	30.9		30.2	27.4	27.4	24.3	
≥6,000 USD	32.3	31.9	35.0	35.6		30.7	31.5	29.2	22.9	
Unknown	13.0	14.0	11.9	13.4		17.4	21.1	18.8	17.1	
Cigarette smoking (cigarettes/day) <sup>b</sup>					<0.001					<0.001
Non-smoker	46.1	42.4	25.6	16.7		96.2	95.3	83.9	77.1	
Ex-smoker	28.8	31.3	34.7	34.3		2.0	2.6	8.6	8.6	
Current smoker (<10)	24.7	26.1	39.3	48.7		2.0	2.1	7.2	14.3	
Current smoker (≥10)	0.2	0.2	0.4	0.3		0.2	0.1	0.3	0.0	
Physical activity <sup>b</sup>					<0.001					0.010
Inactive	41.9	43.9	46.2	48.6		50.7	52.4	58.5	55.7	

Minimally active	50.8	49.3	46.5	42.7		42.0	39.4	32.7	28.6	
HEPA	7.4	6.8	7.3	8.8		7.4	8.2	8.9	15.7	
Adult height (cm) <sup>a</sup>	173.2 (5.8)	173.0 (5.6)	173.3 (5.6)	173.4 (5.5)	<0.001	160.4 (5.2)	160.4 (5.2)	160.7 (5.2)	161.3 (4.5)	0.290
Anti-diabetic medications <sup>b</sup>	2.9	2.6	2.8	4.3	<0.001	2.2	1.0	0.5	1.4	0.015
Anti-hypertensive medications <sup>b</sup>	7.3	6.7	8.6	11.5	<0.001	4.7	3.6	2.7	5.7	0.212
Anti-dyslipidemic medications <sup>b</sup>	4.6	4.2	4.4	5.1	0.160	2.4	2.5	1.3	1.4	0.530
Alcohol flushers <sup>b</sup>	50.8	41.9	18.4	9.2	<0.001	36.9	29.2	11.5	10.0	<0.001

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Data are presented as <sup>a</sup>means (standard deviation), or <sup>b</sup>percentages.  
HEPA, health-enhancing physically active;USD, US dollars.

Supplementary Table 3. Unadjusted associations of alcohol flushing status with cardiovascular risk factors and coronary artery calcium scores in men and women.

Variables	Men				Women			
	Ever-drinkers (n=20 696)	Alcohol flushers (n=5940)	Alcohol non- flushers (n=14 756)	P-value	Ever-drinkers (n=3985)	Alcohol flushers (n=1155)	Alcohol non-flushers (n=2830)	P-value
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	24.7 (2.9)	24.5 (2.8)	24.8 (2.9)	<0.001	22.1 (3.2)	22.1 (3.2)	22.1 (3.2)	0.537
Systolic blood pressure (mmHg) <sup>a</sup>	116.0 (12.4)	114.8 (12.0)	116.5 (12.5)	<0.001	103.6 (12.3)	103.1 (12.0)	103.8 (12.5)	0.097
Diastolic blood pressure (mmHg) <sup>a</sup>	75.2 (10.3)	74.0 (9.7)	75.7 (10.3)	<0.001	66.0 (9.6)	65.3 (9.4)	66.2 (9.7)	0.005
HDL-C (mg/dL) <sup>a</sup>	51.5 (12.1)	50.2 (11.6)	52.1 (12.3)	<0.001	63.4 (14.9)	62.5 (14.9)	63.8 (15.0)	0.021
Total cholesterol (mg/dL) <sup>a</sup>	202.7 (34.5)	201.0 (34.2)	203.4 (34.6)	<0.001	192.3 (33.4)	191.9 (33.4)	192.5 (33.5)	0.526
LDL-C (mg/dL) <sup>a</sup>	129.3 (31.1)	129.9 (31.0)	129.1 (31.2)	0.115	114.0 (30.5)	114.2 (29.8)	113.9 (30.8)	0.787
Triglycerides (mg/dL) <sup>b</sup>	123 (87–175)	118 (84–165)	125 (88–179)	<0.001	75 (57–103)	75 (57–104)	74 (56–103)	0.713
Fasting glucose (mg/dL) <sup>a</sup>	98.2 (16.1)	96.8 (14.4)	98.8 (16.8)	<0.001	92.1 (12.1)	91.9 (13.9)	92.2 (11.4)	0.489
A1C (%) <sup>a</sup>	5.66 (0.53)	5.65 (0.50)	5.67 (0.54)	0.079	5.63 (0.43)	5.63 (0.44)	5.63 (0.43)	0.984
HOMA-IR <sup>b</sup>	1.47 (0.98–2.18)	1.42 (0.97–2.11)	1.49 (0.99–2.21)	<0.001	1.11 (0.76–1.66)	1.12 (0.78–1.68)	1.15 (0.75–1.66)	0.216
CAC score <sup>c</sup>				0.044				0.184
0	17 565 (84.9)	5097 (85.8)	12 468 (84.5)		3866 (97.0)	1129 (97.7)	2737 (96.7)	
1–100	2637 (12.7)	717 (12.1)	1920 (13.0)		109 (2.8)	23 (2.0)	86 (3.0)	
≥101	494 (2.4)	126 (2.1)	368 (2.5)		10 (0.2)	3 (0.3)	7 (0.3)	

Data are presented as <sup>a</sup>means (standard deviation), <sup>b</sup>medians (interquartile range), or <sup>c</sup>percentages.

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; A1C, hemoglobin A1c; CAC, coronary artery calcium; HOMA-IR, homeostasis model assessment of insulin resistance.

For triglycerides and HOMA-IR, Wilcoxon's rank sum test was applied.

Supplementary Table 4. Relationships between lifetime drinking status and covariates among men and women.

Variables	Men			Women		
	Lifetime never-drinkers (n=411)	Ever-drinkers (n=20 696)	P-value	Lifetime never-drinkers (n=738)	Ever-drinkers (n=3985)	P-value
Age (years) <sup>a</sup>	43.3 (9.3)	40.9 (7.0)	<0.001	47.0 (9.4)	39.9 (7.5)	<0.001
Education <sup>b</sup>						
Elementary or less	1.7	0.2	<0.001	5.6	1.7	<0.001
Middle or high school education	12.4	11.5		31.0	25.0	
College or over	85.9	88.3		63.4	73.3	
Monthly household income <sup>b</sup>						
<4,000 USD	23.4	20.5	<0.001	21.5	21.1	0.001
4,000–5,999 USD	27.3	33.2		22.5	28.0	
≥6,000 USD	29.4	33.2		30.6	31.0	
Unknown	19.9	13.1		25.4	19.9	
Cigarette smoking <sup>b</sup>						
Non-smoker	63.0	32.4	<0.001	97.9	94.1	<0.001
Ex-smoker	17.0	32.8		1.0	3.1	
Current smoker	20.0	34.8		1.1	2.8	
Physical activity <sup>b</sup>						
Inactive	48.4	45.3	0.025	51.8	52.6	0.482
Minimally active	41.6	47.3		41.1	39.2	
HEPA	10.0	7.4		7.1	8.2	
Adult height (cm) <sup>a</sup>	172.4 (5.9)	173.2 (5.6)	<0.001	158.9 (5.4)	160.4 (5.2)	0.008
Anti-diabetic medications <sup>b</sup>	2.7	3.0	0.727	3.7	1.2	<0.001
Anti-hypertensive medications <sup>b</sup>	10.2	8.2	0.141	10.7	3.8	<0.001
Anti-dyslipidemic medications <sup>b</sup>	5.8	4.5	0.176	5.8	2.4	<0.001

Data are presented as <sup>a</sup>means (standard deviation), or <sup>b</sup>percentages.  
HEPA, health-enhancing physically active; USD, US dollars.



Supplementary Table 5. Unadjusted associations of lifetime drinking status with cardiovascular risk factors and coronary artery calcium scores.

Variables	Men			Women		
	Lifetime never-drinkers (N=411)	Ever-drinkers (N=20 696)	P-value	Lifetime never-drinkers (N=738)	Ever-drinkers (N=3985)	P-value
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	24.6 (2.9)	24.7 (2.9)	0.448	22.7 (3.2)	22.1 (3.2)	<0.001
Systolic blood pressure (mmHg) <sup>a</sup>	115.0 (11.5)	116.0 (12.4)	0.084	106.9 (14.6)	103.6 (12.3)	<0.001
Diastolic blood pressure (mmHg) <sup>a</sup>	73.4 (9.3)	75.2 (10.3)	<0.001	67.7 (9.8)	66.0 (9.6)	<0.001
HDL-C (mg/dL) <sup>a</sup>	50.3 (12.3)	51.5 (12.1)	0.058	59.9 (14.2)	63.4 (14.9)	<0.001
Total cholesterol (mg/dL) <sup>a</sup>	200.0 (34.2)	202.7 (34.5)	0.109	198.0 (36.9)	192.3 (33.4)	<0.001
LDL-C (mg/dL) <sup>a</sup>	129.7 (30.6)	129.3 (31.1)	0.787	122.2 (33.8)	114.0 (30.5)	<0.001
Triglycerides (mg/dL) <sup>b</sup>	116 (80–167)	123 (87–175)	0.004	84 (61–119)	75 (57–103)	<0.001
Fasting glucose (mg/dL) <sup>a</sup>	97.4 (14.0)	98.2 (16.1)	0.241	94.8 (15.4)	92.1 (12.1)	<0.001
A1C (%) <sup>a</sup>	5.70 (0.52)	5.66 (0.53)	0.143	5.76 (0.54)	5.63 (0.43)	<0.001
HOMA-IR <sup>b</sup>	1.50 (1.03–2.21)	1.47 (0.98–2.18)	0.591	1.16 (0.76–1.78)	1.11 (0.76–1.66)	0.035
CAC score <sup>c</sup>			0.072			<0.001
0	80.8	84.9		90.4	97.0	
1–100	16.3	12.7		7.8	2.8	
≥101	2.9	2.4		1.8	0.2	

Data are presented as <sup>a</sup>means (standard deviation), <sup>b</sup>medians (interquartile range), or <sup>c</sup>percentages.

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol, A1C, hemoglobin A1c; CAC, coronary artery calcium; HOMA-IR, homeostasis model assessment of insulin resistance.

For triglycerides and HOMA-IR, Wilcoxon's rank sum test was applied.