

Supplemental Material

Appendix. KNOW-CKD Investigators

Department of Internal Medicine, Seoul National University, Seoul, Korea	Curie Ahn
	Kook-Hwan Oh
	Soo Kyung Park
	Jayeon Kim
Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea	Dong Wan Chae
	Yun Kyu Oh
	Yong-Soo Kim
Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Korea	Seung Hyeok Han
	Tae-Hyun Yoo
	Kyu Hun Choi
Department of Internal Medicine, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Korea	Kyu-Beck Lee
Department of Internal Medicine, Eulji General Hospital, Eulji School of Medicine, Seoul, Korea	Su ah Sung
Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea	Soo Wan Kim
Department of Internal Medicine, Inje University, Busan Paik Hospital, Busan, Korea	Yeong Hoon Kim
	Sun Woo Kang
Department of Internal Medicine, Seoul Paik Hospital, College of Medicine, Inje University , Seoul, Korea	Ho Seok Koo
Department of Internal Medicine, Gachon University, Gil Hospital, Incheon, Korea	Woogyung Chung
	Jiyong Jung
Department of Prevention and Management, School of Medicine, Inha University, Incheon, Korea	Joongyub Lee

Division of Nephrology, Department of Internal Medicine, National Health Insurance Service Medical Center, Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea	Tae-Ik Chang
Division of Nephrology, Dongtan Sacred Heart Hospital, Hallym University Medical Center, Hwaseong-si, Korea	Ja Ryong Koo
Department of Internal Medicine, Pusan National University School of Medicine, Yangsan, Korea	Eun Young Seong

Data S1.

Supplemental Methods. Data collection and measurements

Demographic data, including age, sex, smoking status, alcohol intake, physical activity, medical history, and presence of comorbid diseases, were obtained from KNOW-CKD database. Based on the smoking status, the participants were classified as never smoked, former smoker, or current smoker. Anthropometric data including height and weight were collected at enrollment. Body mass index was calculated by dividing initial body weight with height squared (kg/m^2). Blood pressure was measured in the sitting position after the subject had been in a relaxed state for at least 5 minutes using an electronic sphygmomanometer. After overnight fasting, blood and urine samples were collected and aliquots of the samples were sent to the central laboratory of KNOW-CKD (Lab Genomics, Seongnam, Korea) for the estimation of serum creatinine and proteinuria. Other biochemical analyses were done at the respective participating centers. The following parameters were estimated: complete blood cell count, fasting glucose, blood urea nitrogen, creatinine, albumin, calcium, phosphorus, high-sensitivity C-reactive protein, and lipid profile including triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Serum high-sensitivity C-reactive protein levels were measured at each center using commercially available enzyme-linked immunosorbent assay kits. Urine protein-to-creatinine ratio was calculated as urine protein concentration divided by urine creatinine concentration (g/g).

Table S1. Baseline characteristics of participants based on HDL-C categories

	HDL-C categories				Total (N=1,864)	P
	<40 mg/dL (N=514)	40-49 mg/dL (N=537)	50-59 mg/dL (N=407)	≥60 mg/dL (N=406)		
Primary kidney disease						<0.001
DMN	184 (35.8%)	148 (27.6%)	61 (15.0%)	69 (17.0%)	462 (24.8%)	
Hypertensive	119 (23.2%)	122 (22.7%)	75 (18.4%)	53 (13.1%)	369 (19.8%)	
Glomerulonephritis	122 (23.7%)	163 (30.4%)	143 (35.1%)	151 (37.2%)	579 (31.1%)	
PKD	51 (9.9%)	65 (12.1%)	96 (23.6%)	111 (27.3%)	323 (17.3%)	
Others	38 (7.4%)	39 (7.3%)	32 (7.9%)	22 (5.4%)	131 (7.0%)	
Comorbidities						
PVD	26 (5.1%)	18 (3.4%)	18 (4.4%)	11 (2.7%)	73 (3.9%)	0.25
CHF	12 (2.3%)	8 (1.5%)	6 (1.5%)	2 (0.5%)	28 (1.5%)	0.16
Laboratory parameters						
Phosphate (mg/dL)	3.7 ± 0.7	3.7 ± 0.7	3.6 ± 0.6	3.8 ± 0.7	3.7 ± 0.7	0.02
PTH (pg/mL)	60.0 (36.9-106.4)	50.9 (33.2-78.6)	48.4 (31.9-76.4)	48.1 (32.3-77.1)	51.2 (33.3-83.7)	<0.001
uACR (mg/g)	325.0 (83.3-927.0)	285.5 (84.6-678.0)	201.7 (41.0-562.6)	155.6 (36.3-574.0)	253.3 (59.2-667.9)	0.003

Table S2. Statistical adjustments for multiple comparisons

	HDL-C category							
	<40 mg/dL		40-49 mg/dL		50-59 mg/dL		≥60 mg/dL	
	HR [95% CI]	P*	HR [95% CI]	P*	HR [95% CI]	P*	HR [95% CI]	P*
	All							
vs. <40 mg/dL	-		1.08 [0.59-1.97]	1.00	1.13 [0.57-2.25]	1.00	0.77 [0.35-1.73]	1.00
vs. 40-49 mg/dL			-		1.05 [0.55-1.98]	1.00	0.72 [0.34-1.50]	1.00
vs. 50-59 mg/dL					-		0.68 [0.32-1.48]	1.00
vs. ≥60 mg/dL							-	
	In the absence of inflammation							
vs. <40 mg/dL	-		0.91 [0.41-2.04]	1.00	0.87 [0.33-2.26]	1.00	0.38 [0.12-1.26]	0.20
vs. 40-49 mg/dL			-		0.95 [0.40-2.28]	1.00	0.42 [0.14-1.25]	0.22
vs. 50-59 mg/dL					-		0.44 [0.15-1.35]	0.32
vs. ≥60 mg/dL							-	
	In the presence of inflammation							
vs. <40 mg/dL	-		1.38 [0.55-3.43]	0.93	1.71 [0.61-4.80]	1.00	2.16 [0.68-6.79]	0.47
vs. 40-49 mg/dL			-		1.23 [0.45-3.38]	1.00	1.56 [0.54-4.53]	1.00

vs. 50-59 mg/dL	-	1.26 [0.41-3.90]	1.00
vs. ≥ 60 mg/dL		-	

Cox proportional-hazards model was constructed to evaluate the associations between serum HDL-C category and eMACE based on the presence of inflammation. The model is adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, diabetes, laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, urine protein-to-creatinine ratio, and medications' use including renin-angiotensin system blockers, diuretics, and statins.

* Corrected using Bonferroni's method due to multiple testing.

CI, confidence interval; eMACE, extended major adverse cardiovascular events; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio.

Table S3. Hazard ratios for the eMACE outcomes based on the HDL-C categories stratified into quartiles overall and in the absence and presence of inflammation

	HDL-C quartiles							
	Q1		Q2		Q3		Q4	
	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P
	All							
Model 1	1.02 [0.64-1.62]	0.93	Reference		1.18 [0.74-1.88]	0.49	0.86 [0.51-1.44]	0.56
Model 2	1.16 [0.71-1.90]	0.54	Reference		1.23 [0.77-1.99]	0.39	0.82 [0.48-1.42]	0.48
Model 3	1.15 [0.70-1.87]	0.59	Reference		1.26 [0.78-2.03]	0.35	0.83 [0.48-1.43]	0.50
	In the absence of inflammation							
Model 1	0.86 [0.49-1.53]	0.61	Reference		0.73 [0.39-1.37]	0.33	0.37 [0.17-0.84]	0.02
Model 2	0.96 [0.53-1.74]	0.89	Reference		0.72 [0.38-1.37]	0.32	0.37 [0.16-0.85]	0.02
Model 3	0.98 [0.54-1.78]	0.95	Reference		0.76 [0.39-1.46]	0.41	0.37 [0.16-0.85]	0.02
	In the presence of inflammation							
Model 1	0.90 [0.44-1.85]	0.77	Reference		0.88 [0.44-1.79]	0.73	1.28 [0.66-2.48]	0.47
Model 2	0.95 [0.45-2.00]	0.89	Reference		0.97 [0.47-1.98]	0.93	1.23 [0.60-2.53]	0.58

Model 3	0.97 [0.46-2.06]	0.93	Reference	0.99 [0.48-2.05]	0.98	1.28 [0.62-2.63]	0.51
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Model 1: adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, and diabetes

Model 2: Model 1 + laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglyceride, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio

Model 3: Model 2 + medications' use including renin-angiotensin system blockers, diuretics, and statins

CI, confidence interval; eMACE, extended major adverse cardiovascular events; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation

Table S4. Hazard ratios for the eMACE outcomes based on the HDL-C categories using a different hsCRP cutoff value for the status of inflammation

	HDL-C category							
	<40 mg/dL		40-49 mg/dL		50-59 mg/dL		≥60 mg/dL	
	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P
In the absence of inflammation								
Model 1	0.62 [0.28-1.36]	0.24	Reference		0.64 [0.29-1.41]	0.27	0.34 [0.13-0.88]	0.03
Model 2	0.65 [0.29-1.49]	0.31	Reference		0.59 [0.26-1.36]	0.22	0.38 [0.14-1.01]	0.05
Model 3	0.63 [0.27-1.45]	0.27	Reference		0.60 [0.26-1.39]	0.23	0.36 [0.14-0.95]	0.04
In the presence of inflammation								
Model 1	1.00 [0.60-1.67]	1.00	Reference		1.30 [0.73-2.33]	0.37	1.26 [0.65-2.43]	0.49
Model 2	0.97 [0.57-1.67]	0.93	Reference		1.29 [0.71-2.34]	0.40	1.15 [0.58-2.27]	0.69
Model 3	0.98 [0.57-1.68]	0.94	Reference		1.33 [0.73-2.42]	0.35	1.18 [0.60-2.33]	0.63

The cutoff value as hsCRP level ≥ 0.6 mg/L, which was the median value, was used.

Model 1: adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, and diabetes

Model 2: Model 1 + laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglyceride, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio

Model 3: Model 2 + medications' use including renin-angiotensin system blockers, diuretics, and statins

CI, confidence interval; eMACE, extended major adverse cardiovascular events; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; SD, standard deviation

Table S5. Time-varying model for risk of eMACE with lipid-lowering drugs treated as a time-varying covariate

	HDL-C per SD		HDL-C category							
			<40 mg/dL		40-49 mg/dL		50-59 mg/dL		≥60 mg/dL	
	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P
All										
Model 1	0.83 [0.67-1.05]	0.13	0.89 [0.56-1.40]	0.61	Reference	0.91 [0.54-1.52]	0.72	0.61 [0.33-1.13]	0.12	
Model 2	0.80 [0.95-1.03]	0.09	0.90 [0.56-1.46]	0.68	Reference	0.91 [0.54-1.53]	0.71	0.59 [0.31-1.12]	0.11	
Model 3	0.81 [0.63-1.04]	0.10	0.89 [0.55-1.43]	0.62	Reference	0.92 [0.54-1.55]	0.75	0.59 [0.31-1.11]	0.10	
In the absence of inflammation										
Model 1	0.71 [0.52-0.98]	0.04	0.91 [0.47-1.75]	0.78	Reference	1.00 [0.50-2.02]	1.00	0.36 [0.14-0.94]	0.04	
Model 2	0.65 [0.45-0.93]	0.02	1.01 [0.51-2.01]	0.97	Reference	0.96 [0.47-1.99]	0.92	0.35 [0.13-0.93]	0.04	
Model 3	0.65 [0.45-0.94]	0.02	1.04 [0.52-2.06]	0.91	Reference	1.01 [0.49-2.10]	0.98	0.36 [0.13-0.96]	0.04	
In the presence of inflammation										
Model 1	1.10 [0.81-1.51]	0.54	0.81 [0.42-1.55]	0.52	Reference	0.88 [0.41-1.91]	0.75	1.36 [0.59-3.11]	0.47	
Model 2	1.13 [0.82-1.56]	0.47	0.69 [0.34-1.37]	0.29	Reference	0.85 [0.38-1.93]	0.70	1.37 [0.58-3.27]	0.48	
Model 3	1.13 [0.82-1.55]	0.45	0.68 [0.34-1.36]	0.28	Reference	0.91 [0.40-2.07]	0.83	1.35 [0.57-3.20]	0.50	

Model 1: adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, diabetes, and medication use of statin

Model 2: Model 1 + laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglyceride, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio

Model 3: Model 2 + medications' use including renin-angiotensin system blockers, and diuretics

CI, confidence interval; eMACE, extended major adverse cardiovascular events; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation

Table S6. Hazard ratios for non-fatal MACE based on the HDL-C levels in the absence and presence of inflammation

	HDL-C per SD		HDL-C category							
			<40 mg/dL		40-49 mg/dL		50-59 mg/dL		≥60 mg/dL	
	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P
All										
Model 1	0.88 [0.71-1.09]	0.23	0.96 [0.61-1.51]	0.87	Reference	1.11 [0.67-1.82]	0.69	0.75 [0.42-1.34]	0.34	
Model 2	0.83 [0.45-1.30]	0.11	1.01 [0.63-1.63]	0.97	Reference	1.12 [0.67-1.83]	0.68	0.70 [0.39-1.27]	0.24	
Model 3	0.84 [0.67-1.06]	0.15	0.98 [0.61-1.58]	0.94	Reference	1.13 [0.69-1.87]	0.63	0.70 [0.39-1.28]	0.25	
In the absence of inflammation										
Model 1	0.74 [0.55-0.99]	0.04	0.98 [0.53-1.80]	0.95	Reference	0.92 [0.48-1.78]	0.81	0.43 [0.19-1.00]	0.05	
Model 2	0.67 [0.48-0.94]	0.02	1.09 [0.58-2.05]	0.79	Reference	0.87 [0.44-1.71]	0.68	0.42 [0.18-0.98]	0.04	
Model 3	0.67 [0.48-0.94]	0.02	1.09 [0.58-2.06]	0.79	Reference	0.89 [0.45-1.78]	0.75	0.41 [0.17-0.97]	0.04	
In the presence of inflammation										
Model 1	1.17 [0.87-1.57]	0.30	0.93 [0.47-1.88]	0.85	Reference	1.43 [0.67-3.08]	0.36	1.70 [0.74-3.90]	0.21	
Model 2	1.12 [0.82-1.53]	0.47	0.84 [0.40-1.74]	0.63	Reference	1.47 [0.67-3.20]	0.34	1.54 [0.64-3.70]	0.33	
Model 3	1.13 [0.83-1.53]	0.44	0.86 [0.41-1.80]	0.70	Reference	1.54 [0.70-3.36]	0.28	1.58 [0.66-3.77]	0.30	

Model 1: adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, and diabetes

Model 2: Model 1 + laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio

Model 3: Model 2 + medications' use including renin-angiotensin system blockers, diuretics, and statins

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MACE, major adverse cardiovascular events; SD, standard deviation

Table S7. Hazard ratios for all-cause mortality based on the HDL-C levels in the absence and presence of inflammation

	HDL-C per SD		HDL-C category							
			<40 mg/dL		40-49 mg/dL		50-59 mg/dL		≥60 mg/dL	
	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P	HR [95% CI]	P
All										
Model 1	0.91 [0.72-1.16]	0.44	1.35 [0.80-2.26]	0.26	Reference		1.13 [0.62-2.06]	0.70	0.88 [0.46-1.71]	0.71
Model 2	0.99 [0.77-1.26]	0.91	1.24 [0.72-2.16]	0.44	Reference		1.12 [0.60-2.09]	0.73	0.93 [0.47-1.81]	0.82
Model 3	1.01 [0.79-1.29]	0.95	1.18 [0.68-2.05]	0.57	Reference		1.16 [0.62-2.16]	0.65	0.92 [0.47-1.80]	0.82
In the absence of inflammation										
Model 1	0.79 [0.56-1.13]	0.20	1.56 [0.73-3.36]	0.25	Reference		1.08 [0.44-2.66]	0.87	0.67 [0.24-1.82]	0.43
Model 2	0.81 [0.54-1.22]	0.32	1.81 [0.78-4.20]	0.16	Reference		1.17 [0.47-2.93]	0.74	0.75 [0.27-2.07]	0.58
Model 3	0.81 [0.54-1.22]	0.32	1.64 [0.70-3.88]	0.26	Reference		1.16 [0.45-3.00]	0.75	0.69 [0.25-1.94]	0.48
In the presence of inflammation										
Model 1	1.12 [0.82-1.53]	0.46	1.02 [0.50-2.07]	0.97	Reference		1.12 [0.49-2.56]	0.78	1.18 [0.49-2.87]	0.71
Model 2	1.26 [0.92-1.72]	0.15	0.75 [0.35-1.60]	0.46	Reference		0.91 [0.38-2.19]	0.84	1.29 [0.51-3.28]	0.59

Model 3	1.26 [0.93-1.71]	0.13	0.70 [0.33-1.48]	0.35	Reference	0.99 [0.41-2.37]	0.98	1.20 [0.48-2.99]	0.70
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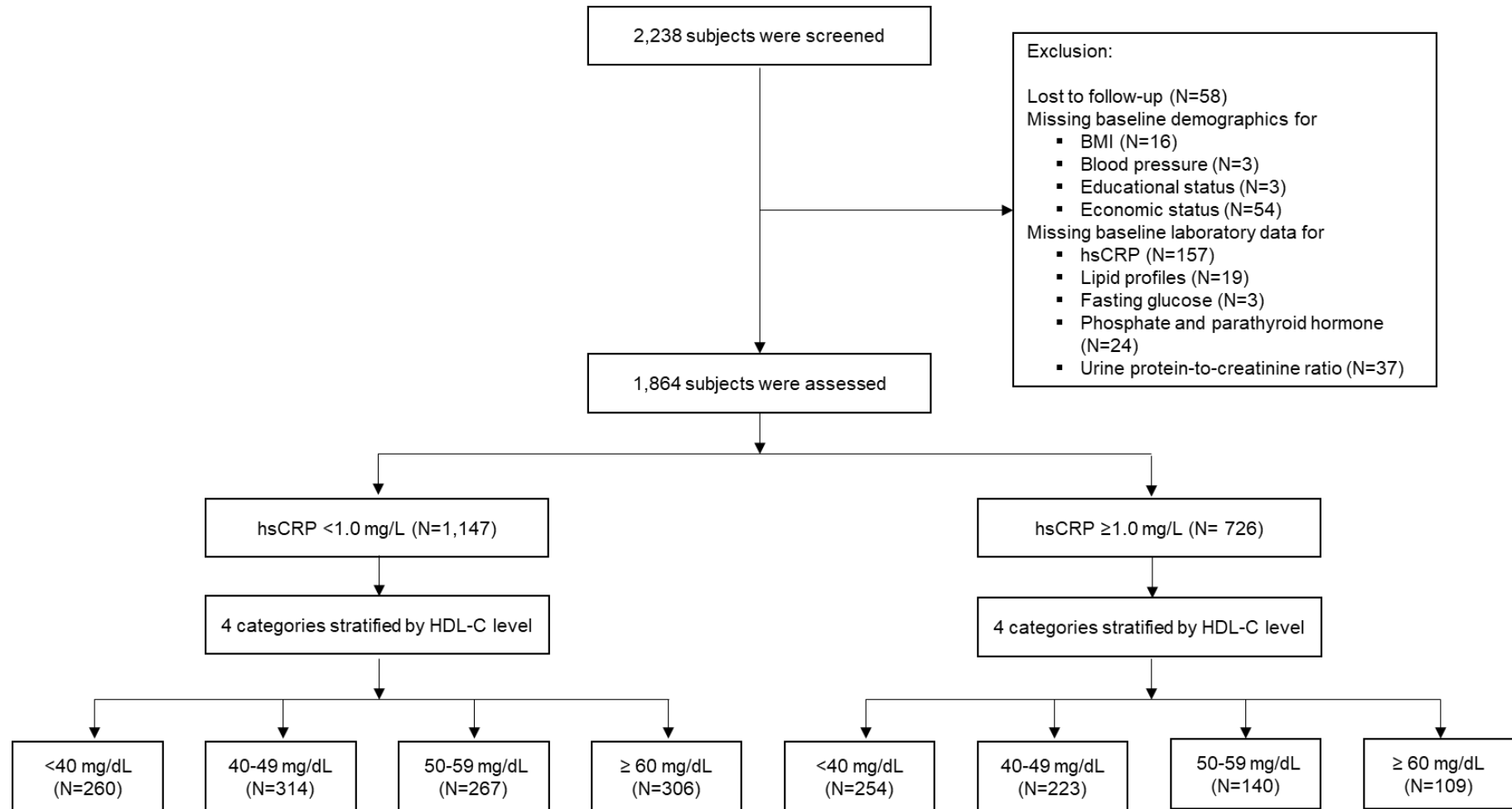
Model 1: adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, and diabetes

Model 2: Model 1 + laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio

Model 3: Model 2 + medications' use including renin-angiotensin system blockers, diuretics, and statins

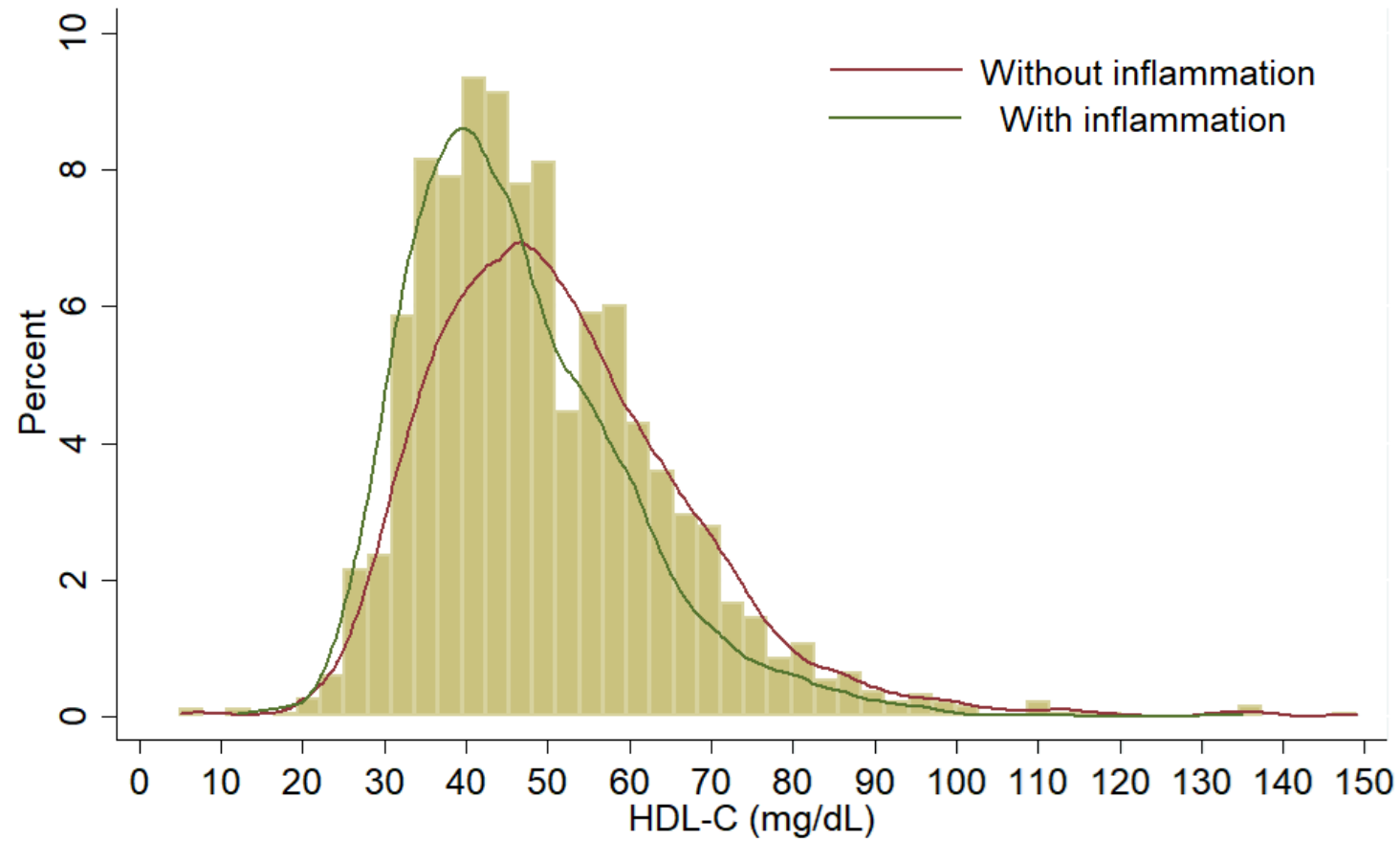
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation

Figure S1. Flow diagram of study participants



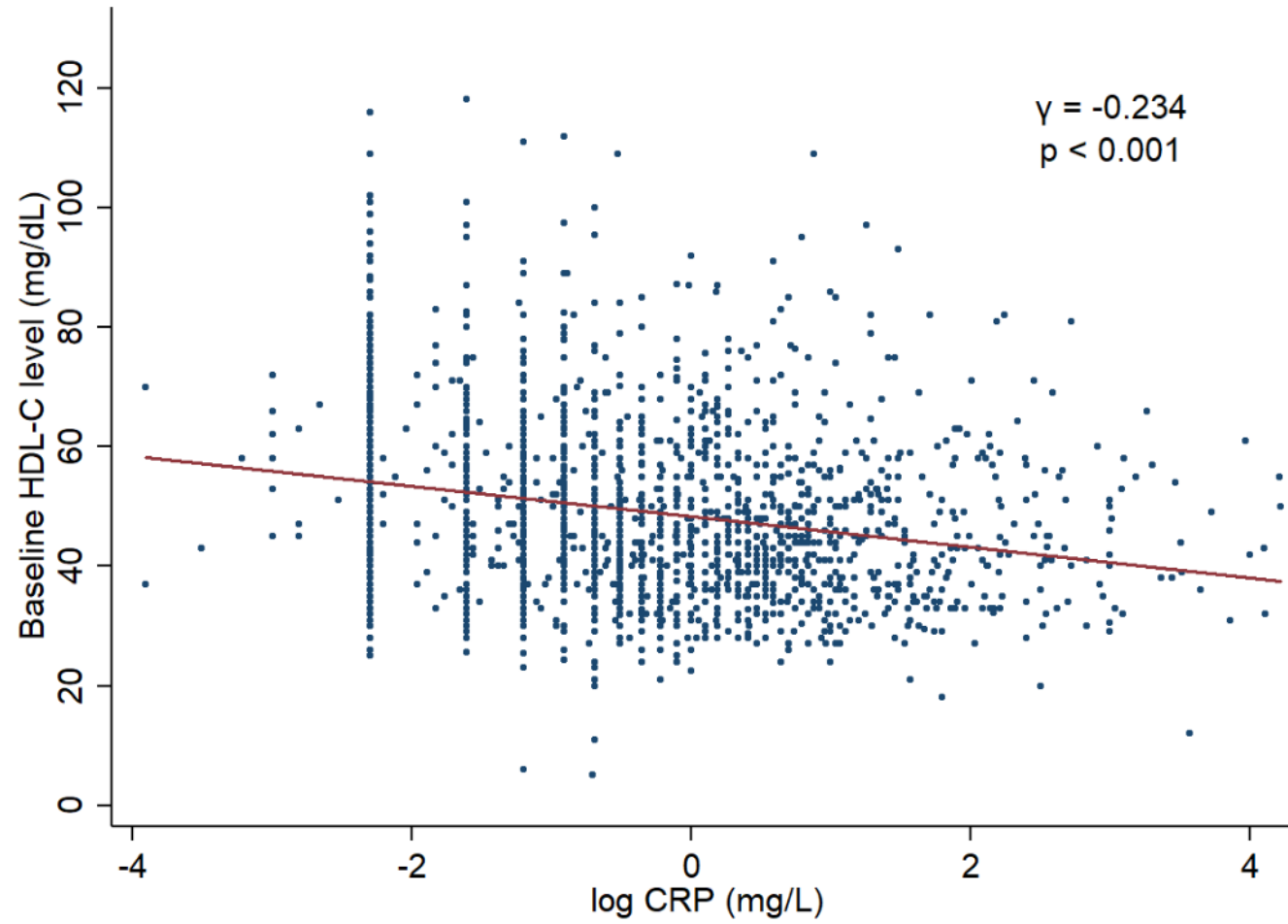
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein

Figure S2. Histogram and kernel density plot showing the distribution of HDL-C



HDL-C, high-density lipoprotein cholesterol

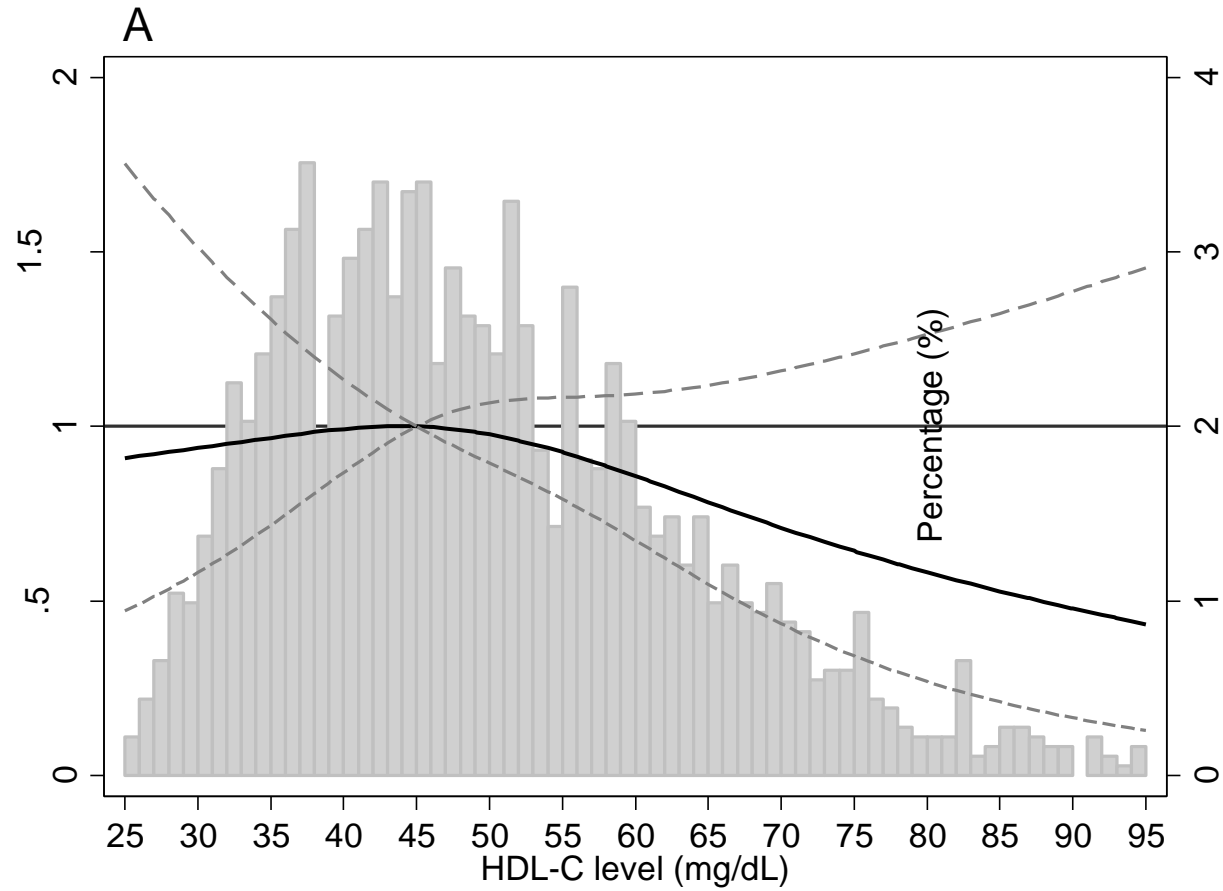
Figure S3. Scatter plot and relationship between the hsCRP and HDL-C levels

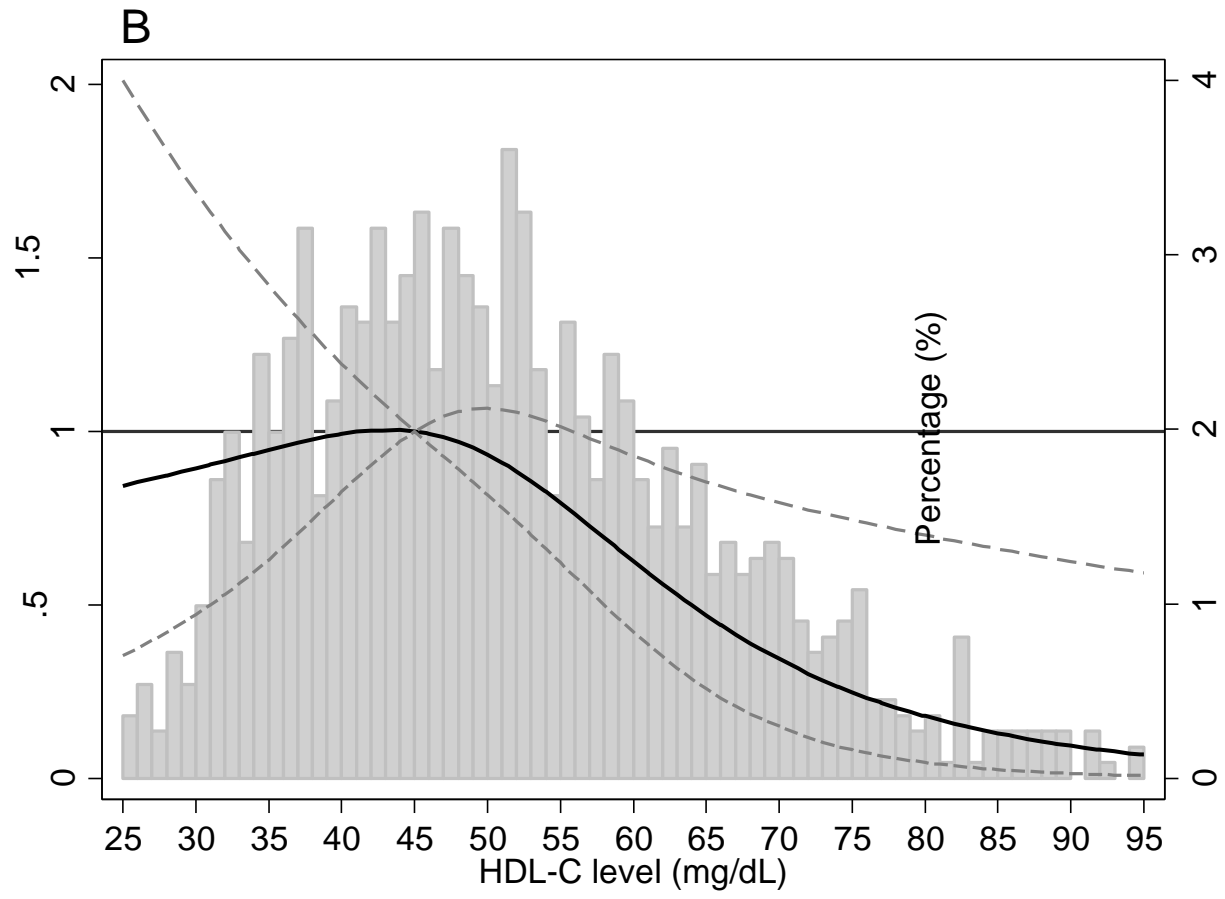


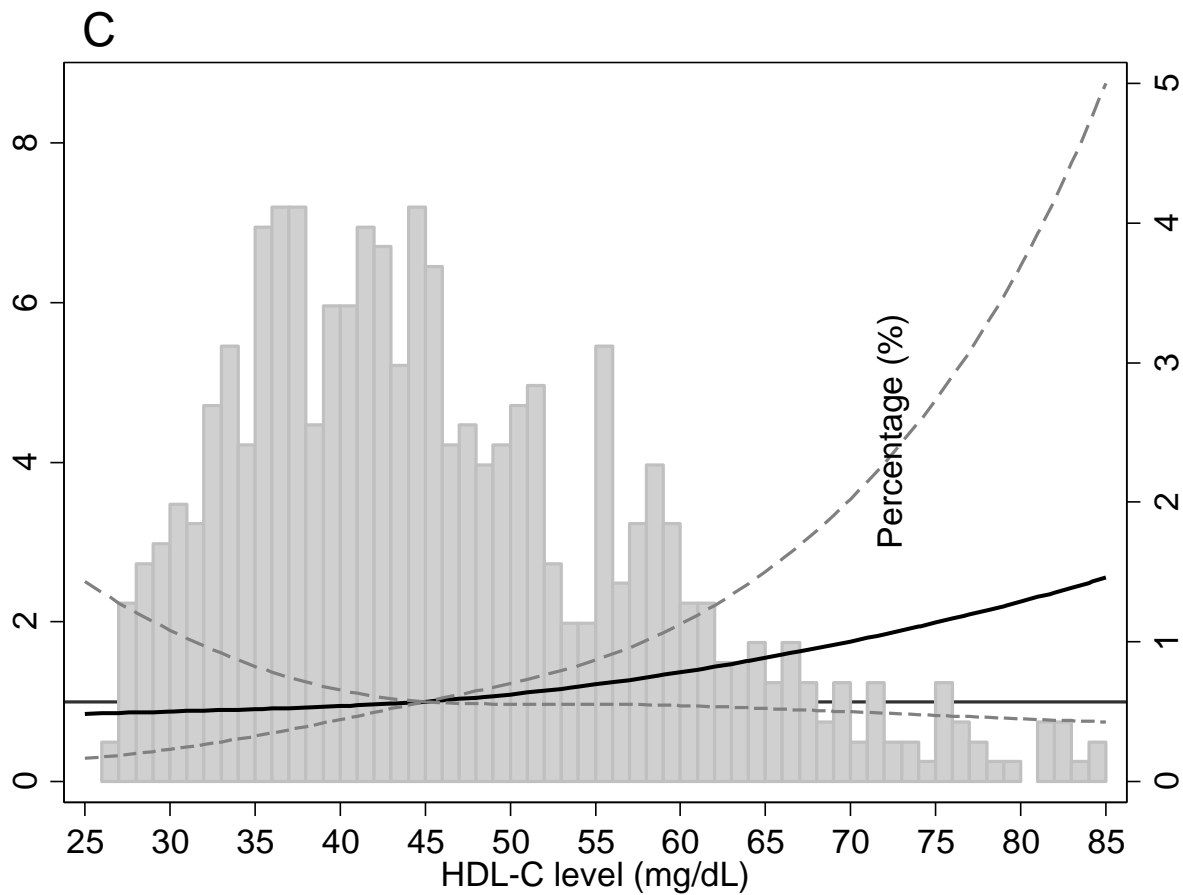
A significant inverse relationship was observed between the HDL-C level and hsCRP level. Linear regression analysis was performed with a curvilinear approach to determine the relationship between the variables.

HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein

Figure S4. Restricted cubic spline curves for the association between the HDL-C level and the risk of eMACE (A) regardless of inflammation, (B) in the absence of inflammation, and (C) in the presence of inflammation





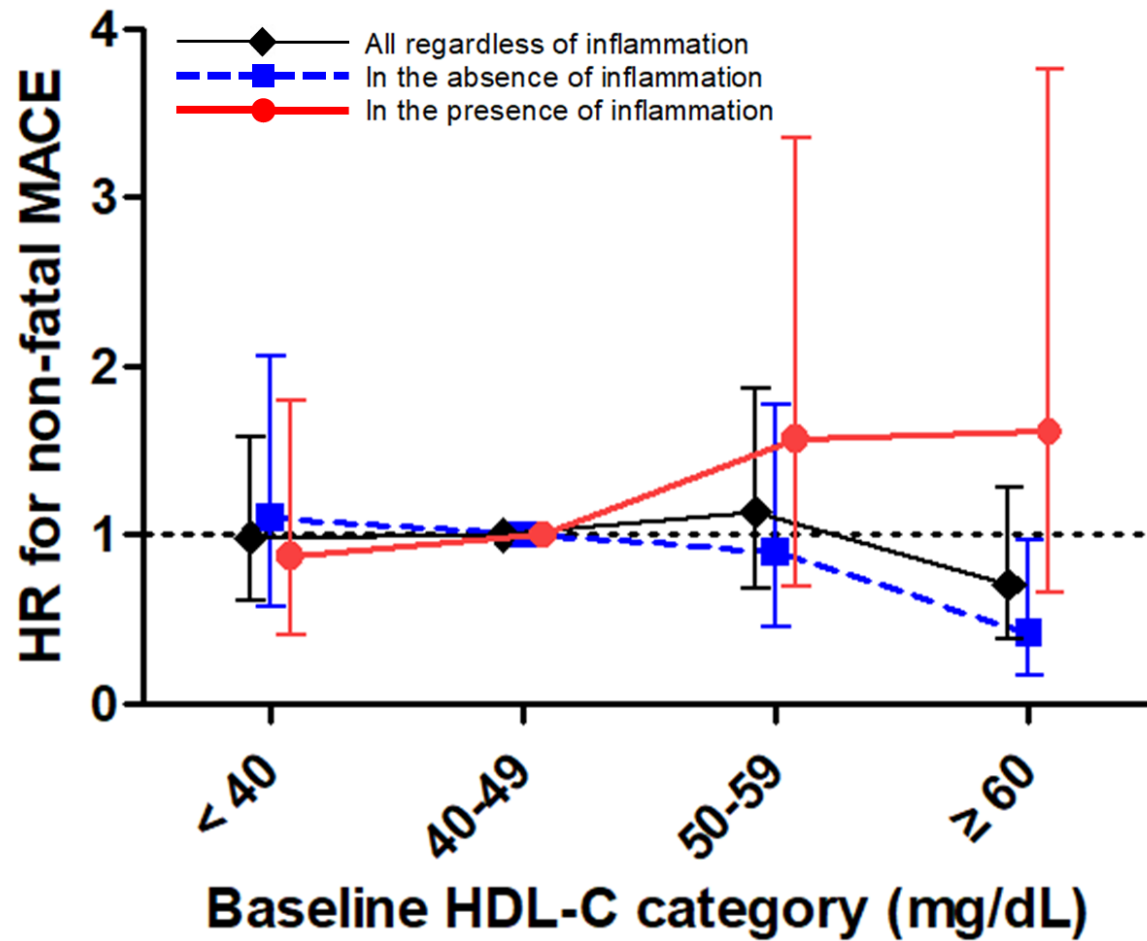


Restricted cubic spline curves for the adjusted hazard ratios show opposite trend for the relationship between HDL-C levels and risk of eMACE in patients with and without inflammation. The model is adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, diabetes, laboratory parameters including fasting blood glucose, low-density lipoprotein

cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, urine protein-to-creatinine ratio, and medications' use including renin-angiotensin system blockers, diuretics, and statins.

eMACE, extended major adverse cardiovascular events; HDL-C, high-density lipoprotein cholesterol

Figure S5. Association of the baseline serum HDL-C level with non-fatal cardiovascular disease

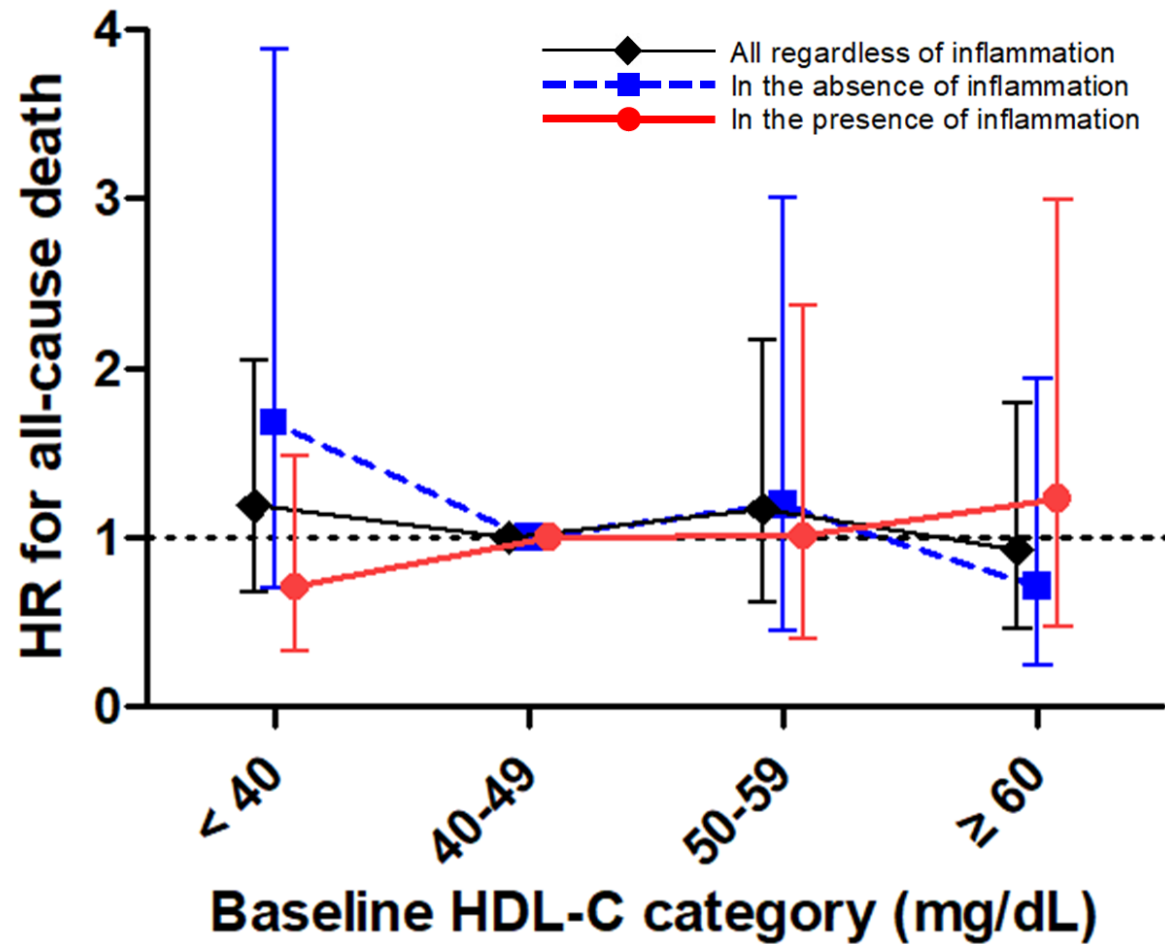


Overall, HDL-C level was not associated with the risk of non-fatal MACE; however, an inverse association was observed in patients without inflammation. This association was reversed without statistical significance in patients with inflammation. Bars represent 95% confidence intervals.

The model is adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, diabetes, laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, urine protein-to-creatinine ratio, and medications' use including renin-angiotensin system blockers, diuretics, and statins.

HDL-C, high density lipoprotein-cholesterol; HR, hazard ratio; MACE, major adverse cardiovascular events

Figure S6. Association of the baseline serum HDL-C level with all-cause mortality

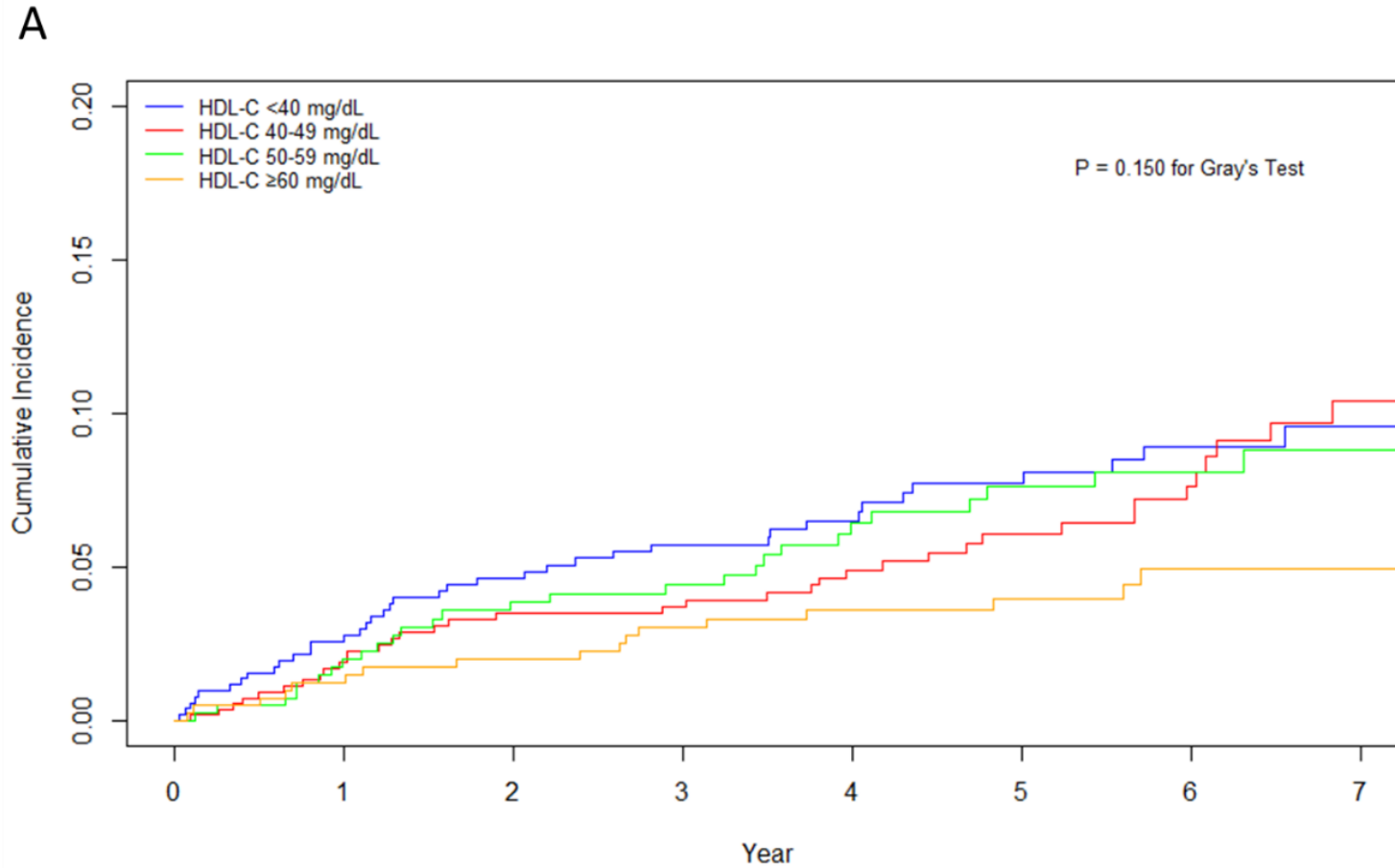


In the analysis for mortality, adjusted HRs were lower in patients without inflammation and with higher HDL-C levels compared to the reference group with HDL-C level of 40–49 mg/dL, but the association was not statistically significant. Bars represent 95% confidence intervals.

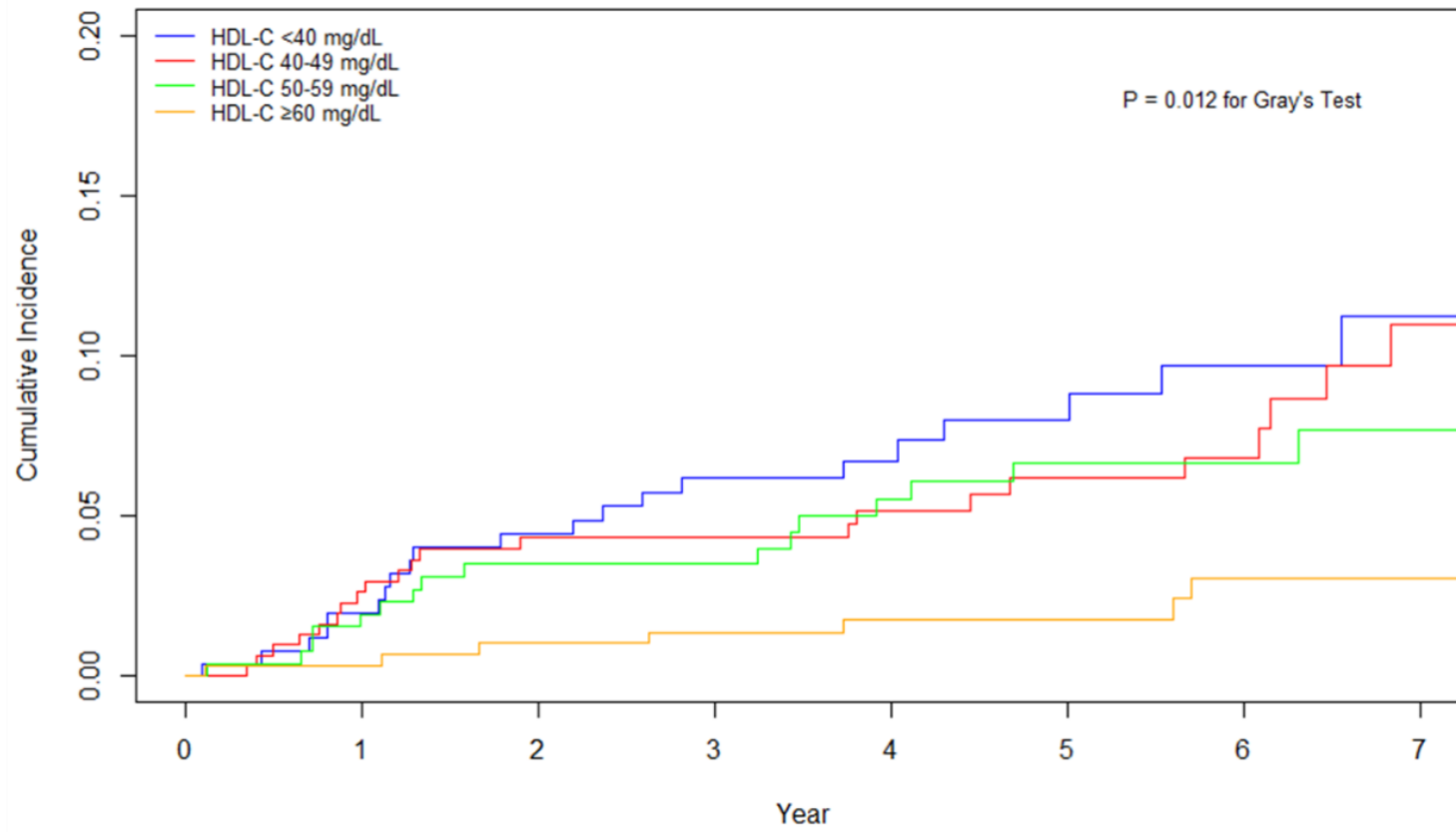
The model is adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease, diabetes, laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, urine protein-to-creatinine ratio, and medications' use including renin-angiotensin system blockers, diuretics, and statins.

HDL-C, high density lipoprotein-cholesterol; HR, hazard ratio

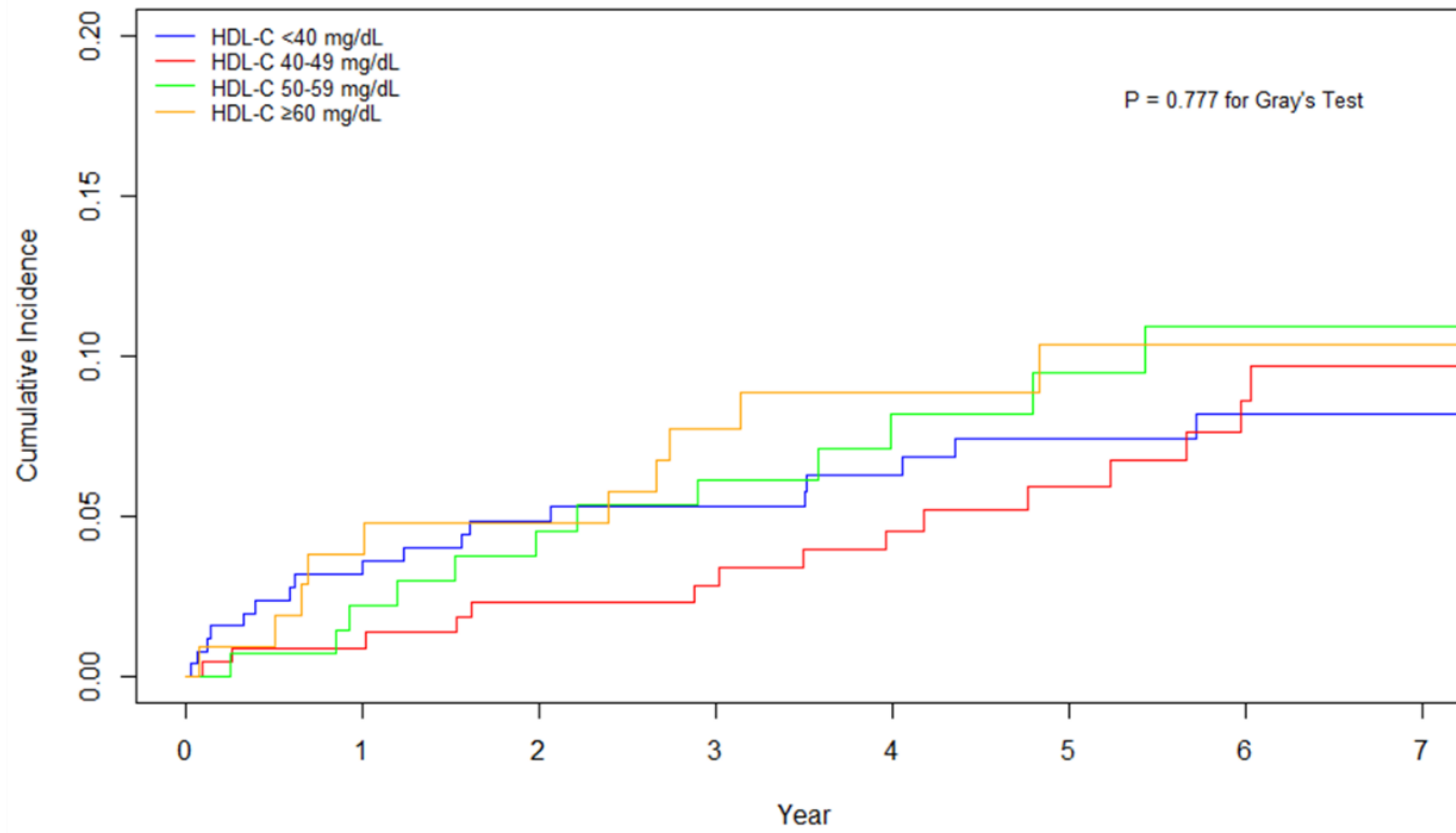
Figure S7. Cumulative incidence curves for non-fatal cardiovascular disease based on the HDL-C categories (A) regardless of inflammation, (B) in the absence of inflammation, and (C) in the presence of inflammation



B

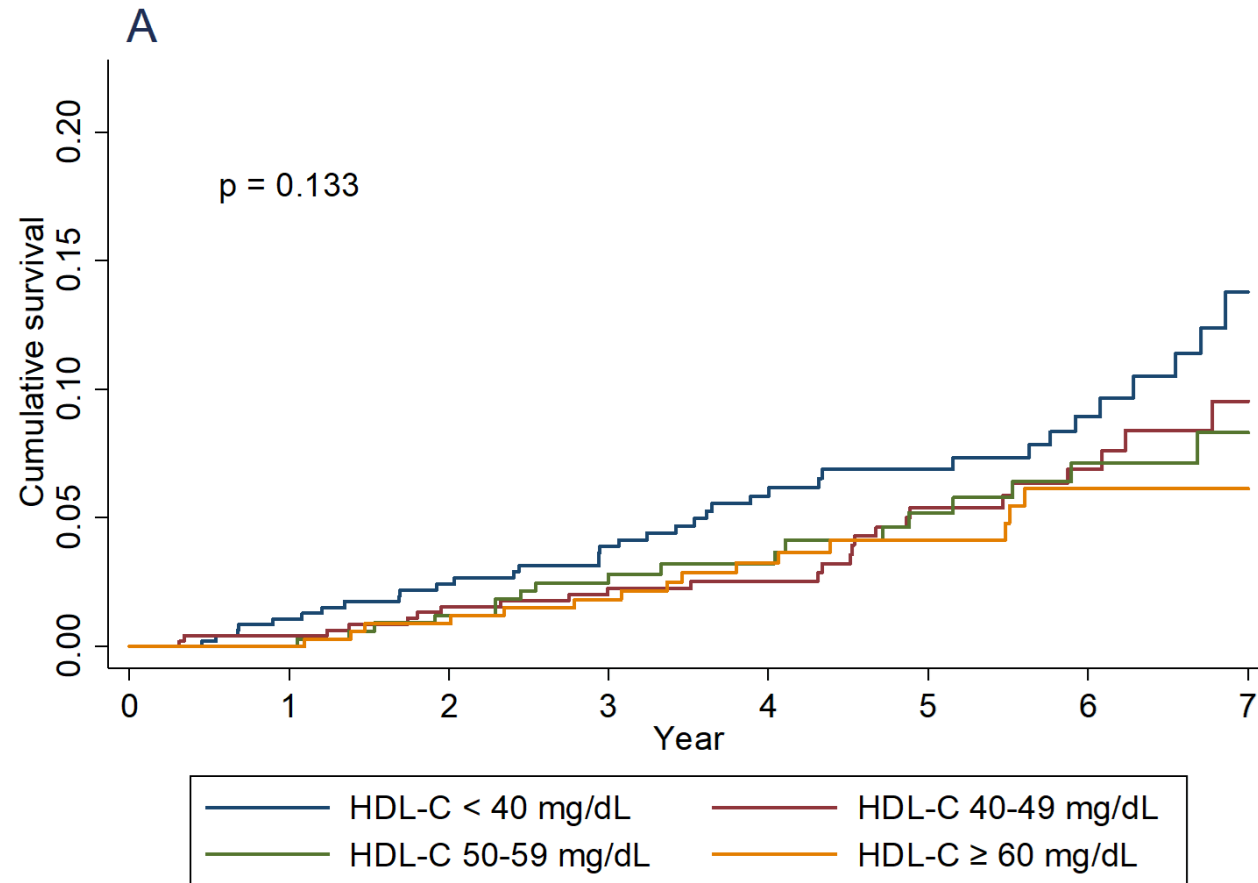


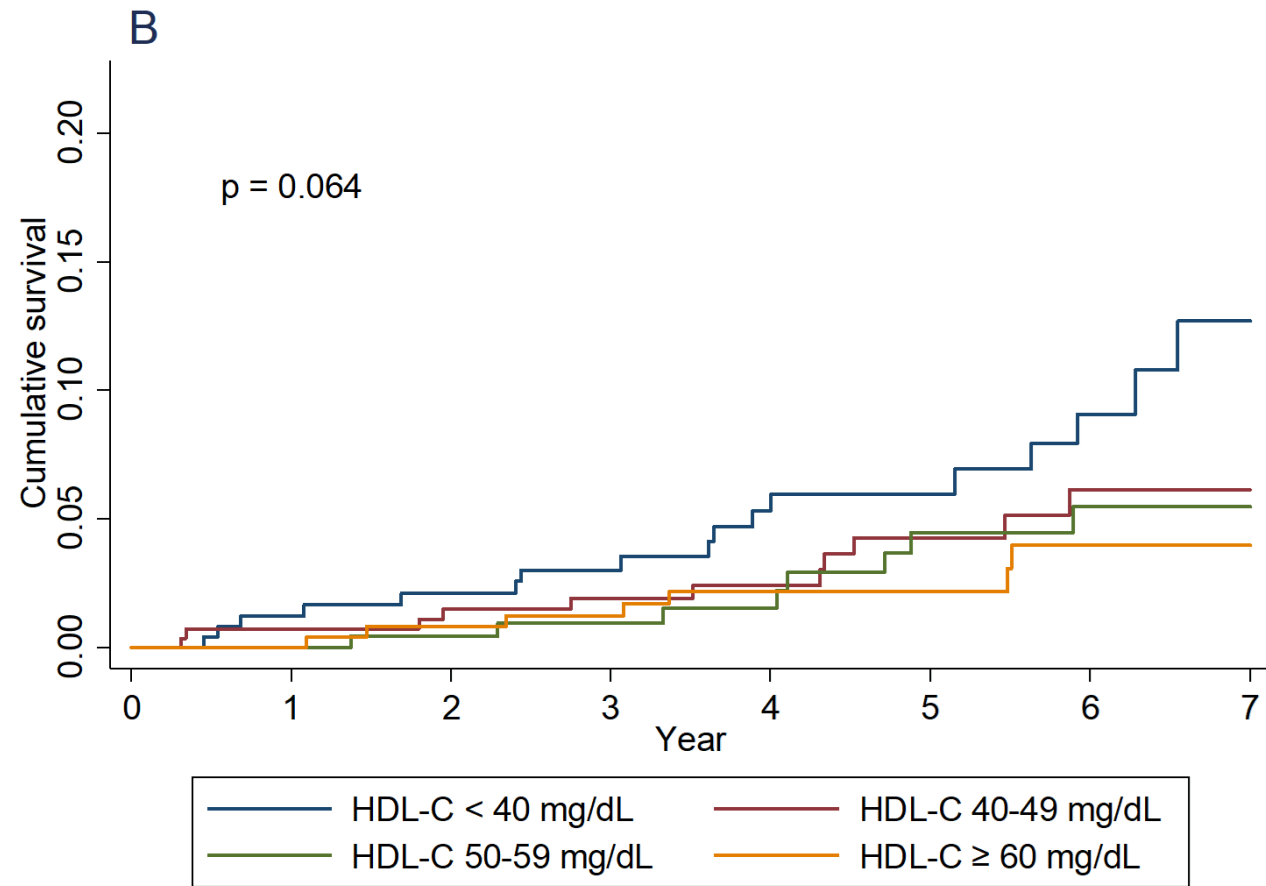
C

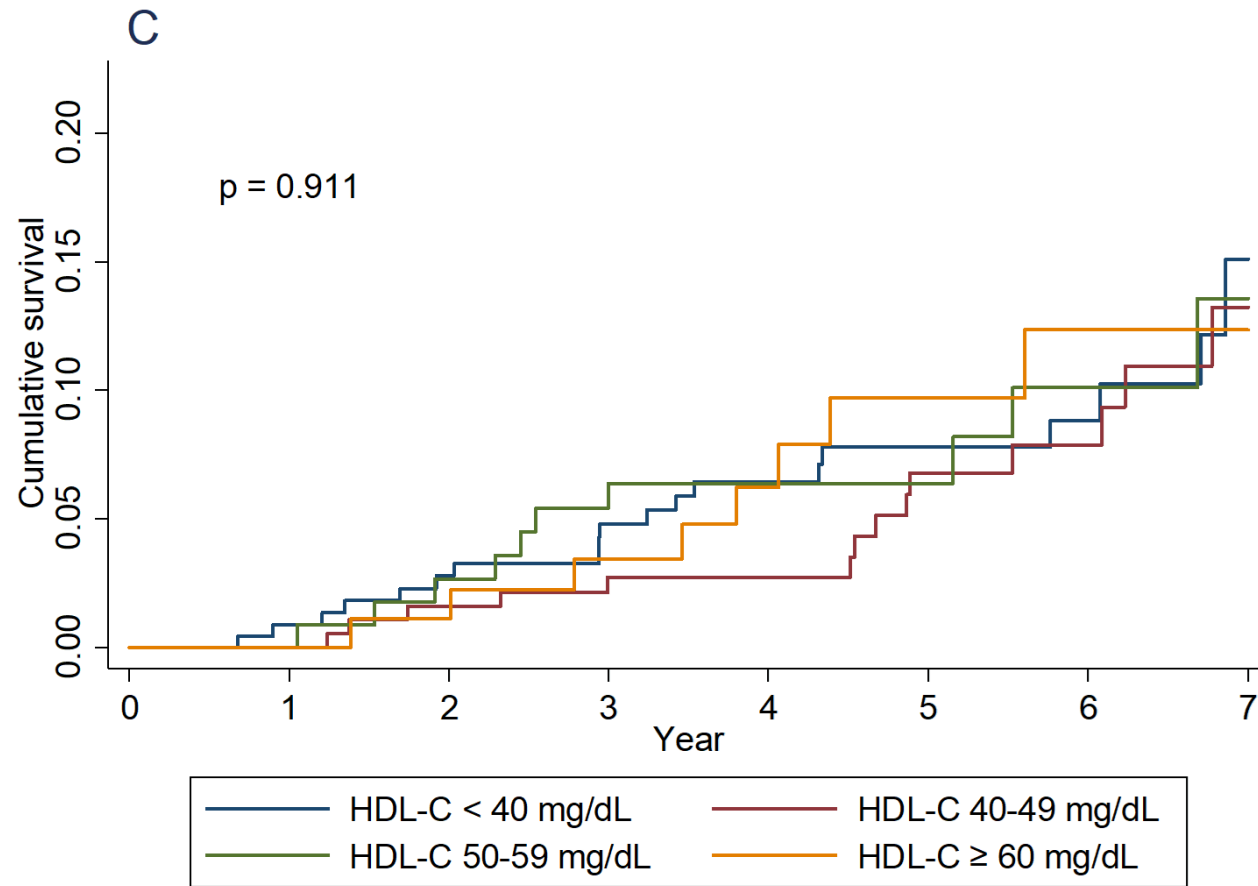


HDL-C, high-density lipoprotein cholesterol

Figure S8. Kaplan-Meier curves for the cumulative incidence of all-cause mortality based on the HDL-C categories (A) regardless of inflammation, (B) in the absence of inflammation, and (C) in the presence of inflammation

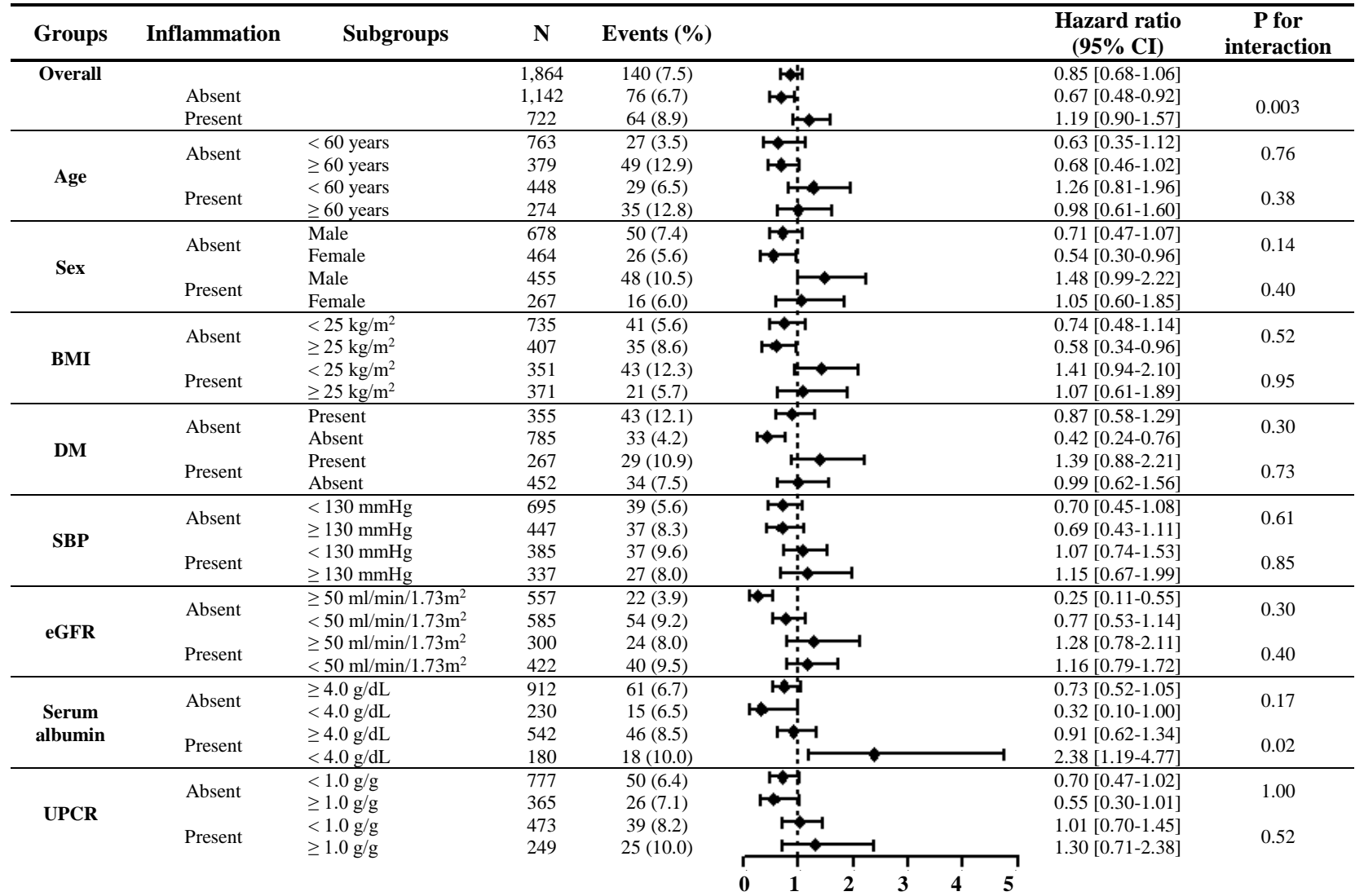






HDL-C, high-density lipoprotein cholesterol

Figure S9. Forest plot for subgroup analysis



The risk modifying effect of inflammation on the relationship between HDL-C level and risk of eMACE existed among most subgroups. Significant interaction was observed between serum albumin level and HDL-C level for eMACE depending on the inflammatory status. Hazard ratios with 95% confidence interval error bars are presented.

The model is adjusted for age, sex, body mass index, smoking status, socioeconomic status, educational status, systolic blood pressure, presence of coronary artery disease and diabetes, laboratory parameters including fasting blood glucose, low-density lipoprotein cholesterol, triglycerides, serum albumin, high-sensitivity C-reactive protein, estimated glomerular filtration rate, urine protein-to-creatinine ratio, and medications' use including renin-angiotensin system blockers, diuretics, and statins.

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; uPCR, urine protein-to-creatinine ratio