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ORIGINAL RESEARCH

Impact of Mean and Variability of High-Density Lipoprotein-Cholesterol on the Risk of Myocardial Infarction, Stroke, and Mortality in the General Population

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BACKGROUND: A low level of high-density lipoprotein-cholesterol (HDL-C) is a well-known risk factor for cardiovascular events. Recent studies have also suggested that HDL-C variability has a predictive role in patients with coronary artery disease. We investigated the combined effect of the mean and variability of HDL-C on the risk of myocardial infarction (MI), stroke, and mortality in the general population.

METHODS AND RESULTS: We selected 5 433 098 subjects in the Korean National Health Insurance System cohort who had no history of MI or stroke and who underwent ≥3 health examinations between 2009 and 2013. Visit-to-visit HDL-C variability was calculated using the coefficient of variation, variability independent of the mean and average real variability. The low-mean and high-variability groups were defined as the lowest and highest quartiles of HDL-C mean and variability, respectively. There were 27 605 cases of MI, 31 162 cases of stroke, and 50 959 deaths during the median follow-up of 5.1±0.6 years. A lower mean or higher variability (coefficient of variation) of HDL-C was associated with a higher risk of adverse outcomes, and the 2 measures had an additive effect. In the multivariable-adjusted model, the hazard ratios (95% CIs) of the low-mean/high-variability group compared with the high-mean/low-variability group were 1.47 (1.41–1.54) for MI, 1.23 (1.18–1.28) for stroke, and 1.41 (1.36–1.45) for all-cause mortality. Results were consistent when variability was modeled using variability independent of the mean or average real variability, and in various sensitivity and subgroup analyses.

CONCLUSIONS: Low mean and high variability of HDL-C is associated with an increased risk of MI, stroke, and mortality.

Key Words: lipoproteins ■ HDL ■ variability ■ myocardial infarction ■ stroke ■ general population ■ epidemiology

Dyslipidemia is recognized as a causative determinant of atherosclerosis. Epidemiological studies have provided evidence that low concentrations of high-density lipoprotein-cholesterol (HDL-C) are associated with an increase in cardiovascular disease (CVD) and mortality.[1] Although there are several well-established risk factors for CVD, other risk factors require further clarification. Recently, a relationship has been identified between visit-to-visit variability in cholesterol levels and various diseases, suggesting that lipid variability is a previously unrecognized residual risk factor for various health outcomes.[2–6] Several studies have demonstrated that the variability of low-density lipoprotein-cholesterol (LDL-C) and HDL-C is associated with a higher risk of developing CVD or of death in subjects with previous coronary artery disease.[2–5]

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CLINICAL PERSPECTIVE

What Is New?

- Low mean high-density lipoprotein-cholesterol (HDL-C) levels and high HDL-C variability was associated with a higher risk for myocardial infarction, stroke, and all-cause mortality.
- Low mean and high variability of HDL-C had additive associations with the risk of cardiovascular outcomes and mortality in the general population.

What Are the Clinical Implications?

- Variability in HDL-C may have a role in predicting cardiovascular outcomes and mortality.
- Treatment strategies to reduce fluctuations in HDL-C might be another goal to prevent adverse health outcomes.

Nonstandard Abbreviations and Acronyms

ARV	average real variability
BMI	body mass index
CV	coefficient of variation
CVD	cardiovascular disease
DM	diabetes mellitus
HDL-C	high-density lipoprotein-cholesterol
HR	hazard ratio
ICD-10	*International Classification of Disease, Tenth Revision*
LDL-C	low-density lipoprotein-cholesterol
MI	myocardial infarction
VIM	variability independent of the mean

Because most patients included in these studies were on statin therapy, incomplete adherence to treatment might have resulted in higher variability in cholesterol. However, because statins have a comparatively small long-term effect on HDL-C, medication noncompliance is a poor explanation for HDL-C variability.[3] Notably, it has also been reported that variability in one lipid measurement, such as LDL-C, triglycerides, or HDL-C, does not always correlate well with variability in the others. In patients with ST-segment–elevation myocardial infarction (MI), the cholesterol efflux and anti-inflammatory properties of HDL-C were significantly dysfunctional.[7] Therefore, it may be necessary to investigate the association between HDL-C variability and CVD events in the general population, not in diseased patients. Because the effect of HDL-C variability alone and in combination with absolute HDL-C levels on the risk of CVD has never been studied, we performed this analysis using a nationwide population-based cohort of >5 million Korean people.

METHODS

All supporting data are available within the article and its online supplementary file.

Data Source

The National Health Insurance System of Korea is a single-payer program that pays costs on the basis of the billing records of healthcare providers. Because membership of the National Health Insurance System is mandatory for all residents in Korea, its 3 main healthcare programs, National Health Insurance, Medical Aid, and Long-Term Care Insurance, cover 100% of the >50 million people in Korea.[8,9] The National Health Insurance System includes an eligibility database (age, sex, socioeconomic variables, type of eligibility, etc), a medical treatment database (based on the accounts submitted by medical service providers for medical expenses), a health examination database (results of general health examinations and questionnaires on lifestyle and behavior), a medical care institution database (types of medical care institutions, location, equipment, and number of physicians), and information about death. Enrollees in the National Health Insurance Corporation are recommended to undergo standardized health examinations every 1 or 2 years.

Study Population

In our study, we screened 19 459 018 people who had undergone a health examination between 2012 and 2013 (index year). We selected 5 632 394 subjects who had undergone a health examination in the index year and ≥2 health examinations in the preceding 3 years. We excluded 435 subjects <20 years old, 34 810 subjects with missing data, and 164 051 subjects with a history of MI [*International Classification of Disease, Tenth Revision* (*ICD-10*) codes: I21, I22] or stroke (*ICD-10* codes: I63, I64) before the index year. Finally, 5 433 098 subjects remained in our study (Figure S1). This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (No. KC18EESI0429). Anonymous and deidentified information was used for analysis, and therefore informed consent was not required.

Measurements and Definitions

Body mass index (BMI), a subject's body weight (kg) divided by the square of their height (m^2), was measured, and obesity was defined as a BMI ≥25 kg/m^2.[10] Regular exercise was defined as performing >20 minutes of strenuous physical activity at least 3 times per week or

>30 minutes of moderate physical activity at least 5 times per week. Household income level was dichotomized at the lowest 25% on the basis of the monthly contributions to National Health Insurance Corporation.[11] We defined the presence of diabetes mellitus (DM) according to the following criteria: (1) at least 1 claim per year under *ICD-10* codes E10 through E14 and at least 1 claim per year for the prescription of antidiabetic medication, or (2) fasting glucose level ≥126 mg/dL. Hypertension was defined as (1) the presence of at least 1 claim per year under *ICD-10* codes I10 or I11 and at least 1 claim per year for the prescription of antihypertensive agents, or (2) systolic/diastolic blood pressure ≥ 140/90 mm Hg. Dyslipidemia was defined as (1) the presence of at least one claim per year under *ICD-10* code E78 and at least 1 claim per year for the prescription of a lipid-lowering agent, or (2) total cholesterol ≥240 mg/dL.

Definition of HDL-C Variability

HDL-C variability was defined as the variability in HDL-C values measured at different health examinations. Three indices of HDL-C variability were used: (1) coefficient of variation (CV), (2) variability independent of the mean (VIM), and (3) average real variability (ARV). CV was calculated as 100%×[SD/mean]. VIM was calculated as $100\%\times(SD/mean^{\beta})$, where β is the regression coefficient, on the basis of the natural logarithm of the SD divided by the natural logarithm of the mean.[12,13] ARV was obtained by calculating the average of the absolute differences between consecutive HDL-C measurements.[14] The number of HDL-C measurements per subject ranged from 3 (n=2 862 984, 52.7%) to 4 (n=2 570 114, 47.3%).

Definition of Low-Mean HDL-C and High HDL-C Variability

Because HDL-C levels differ between men and women, sex-specific cutoff values were used (Table S1). The low-mean HDL-C group was defined as subjects in the lowest quartile (quartile 1) range of mean HDL-C; the other 3 quartile groups (quartiles 2–4) were defined as having high-mean HDL-C. The high-variability group was defined as those subjects in the highest quartile (quartile 4) range of HDL-C variability; the other 3 quartile groups (quartiles 1–3) were defined as having low variability.

Study Outcomes and Follow-Up

The end points of this study were newly diagnosed MI, stroke, or death. MI was defined as the recording of *ICD-10* codes I21 or I22 during hospitalization. Stroke was defined as the recording of *ICD-10* codes I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain computerized tomography. Subjects without MI or stroke during their follow-up period were considered to have completed the study at the date of their death or at the end of follow-up (December 31, 2017), whichever came first. The median follow-up period was 5.1±0.6 years.

Statistical Analysis

Baseline characteristics are presented as the mean±SD, median (25–75%), or n (%). Participants were classified into 4 groups according to quartiles of the mean and variability (CV) of HDL-C. The incidence rate of outcomes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). Hazard ratios (HRs) and 95% CI values for MI, stroke, and all-cause mortality were analyzed using the Cox proportional hazards model. HR (95% CI) of the highest quartile (quartile 4) of HDL-C variability was compared with that of the lower 3 quartiles (quartiles 1–3) as a reference group. HR (95% CI) of the lowest quartile (quartile 1) of mean HDL-C was compared with that of the higher 3 quartiles (quartiles 2–4) as a reference group. The proportional hazards assumption was evaluated by the Schoenfeld residuals test using the logarithm of the cumulative hazards function based on Kaplan–Meier estimates for the quartile groups of mean or variability of HDL-C, or groups based on the combination of mean and variability. There was no significant departure from proportionality of hazards over time. A multivariable-adjusted proportional hazards model was applied adjusting for age, sex, BMI, alcohol drinking, smoking, regular exercise, income status, DM, hypertension, and use of lipid-lowering agent. Sensitivity analysis was performed by excluding subjects with DM, hypertension, and dyslipidemia because the presence of these conditions or consumption of related medications could influence the HDL-C level or its variability. Sensitivity analyses were also performed by excluding subjects with the occurrence of outcomes within 2 years of follow-up, to account for the possibility of reverse causation. The potential effect of modification by age, sex, obesity, DM, hypertension, malignancy, and use of lipid-lowering agents was evaluated through stratified analysis and interaction testing using a likelihood-ratio test. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC), and $P<0.05$ was considered to indicate significance.

RESULTS

Baseline Characteristics of the Study Population

The baseline characteristics of subjects classified according to the mean and variability (CV) of HDL-C are described in Table 1. Subjects were classified

Table 1. Baseline Characteristics of Subjects According to the Mean and Variability (CV) of HDL-C

	High Mean/Low ariability (n=3 057 031)	High Mean/High Variability (n=1 024 571)	Low Mean/Low Variability (n=1 017 774)	Low Mean/High Variability (n=333 722)
Age, y	43.5±11.7	45.7±12.5	46.1±11.6	48.3±12.5
Sex, male	2 000 432 (65.4)	687 518 (67.1)	682 528 (67.1)	206 829 (62.0)
Body mass index, kg/m^2	23.4±3.2	23.6±3.2	24.9±3.2	24.8±3.2
Systolic BP, mm Hg	120.7±13.7	122.0±14.1	122.4±13.7	122.9±14.0
Diastolic BP, mm Hg	75.8±9.6	76.6±9.7	76.8±9.5	76.9±9.6
Fasting glucose, mg/dL	95.3±18.8	97.0±21.9	99.0±23.7	100.0±25.6
Total cholesterol, mg/dL	194.8±30.1	194.6±31.1	190.2±30.8	188.2±30.9
Triglyceride, mg/dL	97 (67–141)	116 (79–175)	141 (97–205)	150 (101–222)
LDL-C, mg/dL	113.7±33.2	112.1±35.7	115.6±35.6	112.6±38.0
HDL-C, mg/dL	59.4 ±11.4	59.9±21.7	42.1±5.9	42.3±9.5
HDL-C mean, mg/dL	59.4±10.1	60.3±14.7	42.1±4.8	42.2±5.0
HDL-C CV, %	9.0±3.7	22.9±12.4	9.0±3.7	21.9±6.6
HDL-C VIM, %	4.6±2.3	11.3±4.4	8.3±3.9	20.4±19.0
HDL-C ARV, mg/dL	6.5±3.4	17.2±20.7	4.6±2.4	11.1±4.5
Current smoker	882 741 (28.9)	312 832 (30.5)	329 851 (32.4)	100 773 (30.2)
Alcohol drinking	261 217 (8.5)	100 534 (9.8)	54 903 (5.4)	19 317 (5.8)
Regular exercise	654 530 (21.4)	224 762 (21.9)	198 270 (19.5)	66 041 (19.8)
Income (lower 25%)	496 581 (16.2)	204 074 (19.9)	175 051 (17.2)	72 788 (21.8)
Diabetes mellitus	166 191 (5.4)	80 305 (7.8)	103 606 (10.2)	41 857 (12.5)
Hypertension	548 832 (18.0)	236 507 (23.1)	248 501 (24.4)	95 709 (28.7)
On lipid-lowering agent	225 573 (7.4)	102 537 (10.0)	108 733 (10.7)	44 963 (13.5)
Any malignancy	45 665 (1.5)	18 739 (1.8)	19 509 (1.9)	7904 (2.4)

Data are expressed as the mean±SD, median (25–75%), or n (%). ARV indicates average real variability; BP, blood pressure; CV, coefficient of variation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and VIM, variability independent of the mean.

into 4 groups: high-mean/low-variability group, high-mean/high-variability group, low-mean/low-variability group, and low-mean/high-variability group. Subjects in the low-mean/high-variability group were older and more likely to be female, had a higher prevalence of DM and hypertension, and were more likely to be taking a lipid-lowering agent and to have lower income. In this group, total cholesterol and LDL-C levels were lower, whereas triglyceride levels were higher than in the other groups. The *P* values for trend were <0.001 for all parameters because of the large size of the study population. Because abnormalities in HDL-C levels are frequently accompanied by obesity or metabolic syndrome, we performed correlation analysis between HDL-C variability and variabilities in other metabolic parameters. The correlations between the CV of HDL-C and the CV of triglycerides (r=0.12), the CV of LDL-C (r=0.19), the CV of fasting blood glucose (r=0.08), and the CV of BMI (r=0.06) were not robust (Table S2).

Risk of Myocardial Infarction According to the Mean and Variability of HDL-C

There were 27 605 cases of new-onset MI (0.51%) during the follow-up period. When the subjects were categorized into quartile groups, both low mean and high variability of HDL-C were associated with a higher incidence rate of MI than for higher-mean and lower-variability groups (Figure 1A). After adjusting for age, sex, BMI, alcohol drinking, smoking, regular exercise, income status, DM, hypertension, and lipid-lowering medication, the risk of MI was 33% higher in the low-mean group and 13% higher in the high-variability group, compared with the high-mean or low-variability groups, respectively. The HR (95% CI) for MI was 1.16 (1.13–1.20) in the high-mean/high-variability group, 1.36 (1.32–1.40) in the low-mean/low-variability group, and 1.47 (1.41–1.54) in the low-mean/high-variability group compared with that in the high-mean/low-variability group. An additive effect of the mean and variability of HDL-C on the risk of MI was identified (Table 2).

Risk of Stroke According to the Mean and Variability of HDL-C

There were 31 162 cases of new-onset stroke (0.57%) during the follow-up period. Similar to MI, both low mean and high variability of HDL-C were associated with a higher incidence rate of stroke than for higher-mean and lower-variability groups, respectively (Figure 1B). After multivariable adjustment, the risk of stroke was

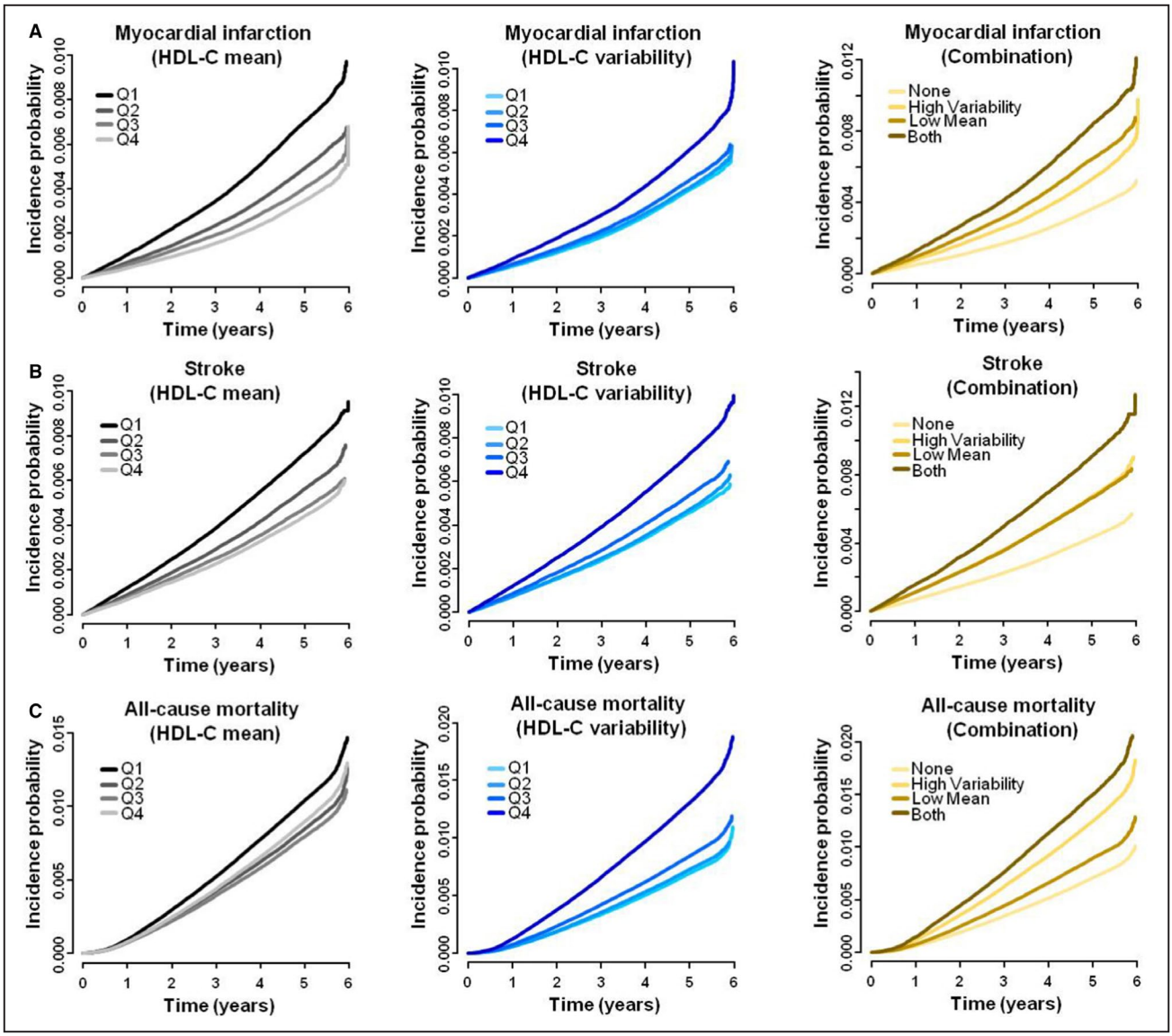

Figure 1. Incidence probability of myocardial infarction (A), stroke (B), and all-cause mortality (C) according to the mean, variability, and combination of mean and variability of HDL-C.
HDL-C indicates high-density lipoprotein cholesterol.

13% higher in the low-mean group and 11% higher in the high-variability group than for the high-mean or low-variability groups, respectively. The HRs (95% CIs) for stroke were 1.15 (1.11–1.18) in the high-mean/high-variability group, 1.16 (1.13–1.20) in the low-mean/low-variability group, and 1.23 (1.18–1.28) in the low-mean/high-variability group than for that in the high-mean/low-variability group (Table 2). Again, this suggests an additive effect of mean and variability of HDL-C on the risk of stroke.

Risk of All-Cause Mortality According to the Mean and Variability of HDL-C

There were 50 959 deaths (0.94%) during the follow-up period. The lowest-mean and highest-variability quartile groups showed the highest incidence rate of mortality (Figure 1C). After multivariable adjustment, the risk of all-cause mortality was 7% higher in the low-mean group and 29% higher in the high-variability group than that in the high-mean or low-variability groups, respectively. The HRs (95% CIs) for mortality were 1.28 (1.26–1.31) in the high-mean/high-variability group, 1.07 (1.04–1.10) in the low-mean/low-variability group, and 1.41 (1.36–1.45) in the low-mean/high-variability group compared with that in the high-mean/low-variability group (Table 2).

Sensitivity Analysis

The results were largely consistent when further adjusting for triglyceride levels or triglyceride variability

Table 2. Risk of MI, Stroke, and Mortality According to the Mean and Variability (CV) of HDL-Cholesterol

	MI			Stroke			Mortality		
	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)
Mean									
High mean (Q2–4)	17 784	0.85	1 (ref.)	20 990	1.00	1 (ref.)	36 195	1.73	1 (ref.)
Low mean (Q1)	9821	1.42	1.33 (1.29, 1.36)	10 172	1.47	1.13 (1.10, 1.16)	14 764	2.13	1.07 (1.05, 1.09)
Variability									
Low variability (Q1–3)	18 855	0.90	1 (ref.)	20 862	1.00	1 (ref.)	32 273	1.54	1 (ref.)
High variability (Q4)	8750	1.26	1.13 (1.10, 1.16)	10 300	1.49	1.11 (1.09, 1.14)	18 686	2.69	1.29 (1.27, 1.31)
Combination									
High mean/low variability	11 950	0.76	1 (ref.)	13 825	0.88	1 (ref.)	22 787	1.45	1 (ref.)
High mean/high variability	5834	1.12	1.16 (1.13, 1.20)	7165	1.37	1.15 (1.11, 1.18)	13 408	2.56	1.28 (1.26, 1.31)
Low mean/low variability	6905	1.32	1.36 (1.32, 1.40)	7037	1.35	1.16 (1.13, 1.20)	9486	1.81	1.07 (1.04, 1.10)
Low mean/high variability	2916	1.71	1.47 (1.41, 1.54)	3135	1.84	1.23 (1.18, 1.28)	5278	3.09	1.41 (1.36, 1.45)

Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension, and use of lipid lowering agent. CV indicates coefficient of variation; HR, hazard ratio; and MI, myocardial infarction.
*Per 1000 person-years.

in addition to the original model (Table S3). The results were also similar when the variability of HDL-C was determined using VIM or ARV (Tables S4 and S5). After excluding subjects with DM, hypertension, and dyslipidemia, the respective and combined effects of mean and variability of HDL-C on MI, stroke, and mortality were similar to those in the whole cohort (Table 3). Excluding subjects with the occurrence of outcomes within 2 years of follow-up did not change the association between mean and variability of HDL-C and outcomes (Table S6). Similar results were noted when performing an analysis with subjects who had participated in 4 yearly health examinations (Table S7).

Subgroup Analysis

We also performed stratified analysis by age, sex, presence or absence of obesity, DM, hypertension, malignancy, and use of lipid-lowering agents; *P* values for interaction are shown in Figure 2. The significant associations of a low mean and high variability of HDL-C with the risk of MI, stroke, and all-cause mortality were present in almost all subgroups. The association between high variability of HDL-C and outcomes was stronger in nonobese subjects and nonusers of lipid-lowering medications.

DISCUSSION

In this nationwide population-based cohort study, we demonstrated that low mean and high variability of HDL-C are associated with the risk of all-cause mortality, MI, and stroke during a 5-year follow-up period. This is the first study to clarify the relationship between HDL-C variability and cardiovascular outcomes in the general population. We also found that the mean and variability of HDL-C had an additive effect on the risks of all-cause mortality, MI, and stroke.

We previously reported that high variability in total cholesterol levels was an independent predictor of adverse cardiovascular events among the general population.[6] Despite the fact that lipid parameters are closely related, the correlations between the variabilities of lipid parameters were not robust. The present study suggests that variability in HDL-C, a widely measured cholesterol fraction, is also an indicator of a high risk of developing CVD and of all-cause mortality. Environmental factors, including diet, smoking, alcohol intake, obesity, and physical activity, can affect HDL-C levels.[15,16] Changes between successive evaluations (lack of physical activity, lifestyle changes, or preclinical illness) could have an impact on an individual's HDL-C and be causally associated with adverse outcomes and HDL-C variability. A low HDL-C is often accompanied by obesity

Table 3. Risk of MI, Stroke and Mortality According to the Mean and Variability (CV) of HDL-C (Sensitivity Analysis Excluding Subjects With Diabetes Mellitus, Hypertension, and Dyslipidemia)

	MI			Stroke			Mortality		
	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)
Mean									
High mean (Q2–4)	8368	0.53	1 (ref.)	8367	0.53	1 (ref.)	16 911	1.07	1 (ref.)
Low mean (Q1)	3911	0.85	1.31 (1.26, 1.37)	3387	0.74	1.13 (1.08, 1.18)	5641	1.22	1.06 (1.03, 1.10)
Variability									
Low variability (Q1–3)	8799	0.56	1 (ref.)	8287	0.53	1 (ref.)	15 100	0.97	1 (ref.)
High variability (Q4)	3480	0.73	1.13 (1.09, 1.18)	3467	0.73	1.13 (1.08, 1.17)	7452	1.57	1.32 (1.28, 1.36)
Combination									
High mean/low variability	5934	0.49	1 (ref.)	5830	0.48	1 (ref.)	11 261	0.93	1 (ref.)
High mean/high variability	2434	0.66	1.15 (1.10, 1.21)	2537	0.69	1.16 (1.10, 1.21)	5650	1.53	1.32 (1.28, 1.37)
Low mean/low variability	2865	0.81	1.34 (1.28, 1.40)	2457	0.69	1.16 (1.11, 1.22)	3839	1.08	1.07 (1.03, 1.11)
Low mean/high variability	1046	0.99	1.47 (1.37, 1.57)	930	0.88	1.23 (1.14, 1.31)	1802	1.69	1.41 (1.34, 1.49)

Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise and income status. CV indicates coefficient of variation; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; and MI, myocardial infarction.
*Per 1000 person-years.

and elevated triglyceride levels. It is possible that BMI and triglyceride variability over time are responsible for the related variability in HDL-C. However, we performed correlation analysis and found that the correlation coefficient between HDL-C variability and triglycerides (r=0.12) or BMI (r=0.06) variability was relatively low. We found that the associations between HDL-C variability and adverse outcomes persisted after adjustment for variables including alcohol drinking, smoking, physical activity, and triglyceride levels or triglyceride variability. There may also be other mechanisms that can explain the link between HDL-C variability and adverse health outcomes.

In terms of the risk of MI, the mean HDL-C level seems to be more important than its variability, although high variability of HDL-C may play a bigger role in the risk of all-cause mortality. The multivariable adjusted HRs of the low-mean group compared with the high-mean group were 1.33 (1.29–1.36) for MI and 1.07 (1.05–1.09) for all-cause mortality. The multivariable adjusted HRs of the high-variability group compared with the low-variability group were 1.13 (1.10–1.16) for MI and 1.29 (1.27–1.31) for all-cause mortality. HDL-C has been shown to have a variety of beneficial protective actions on blood vessels, and it has long been considered "good cholesterol."[1] It is well accepted that high HDL-C levels are associated with reduced CVD and mortality, although several recent studies raised the question that extremely high HDL-C levels might be paradoxically associated with high mortality.[17–20] The exact mechanism for the relationship between the high variability of HDL-C and an increased risk of CVDs is unknown. However, high HDL-C variability could cause plaque instability by impairing cholesterol efflux from peripheral tissues and macrophages.[5] The group with a consistently high HDL-C, that is, the high-mean and low-variability group, could represent a healthy population. Higher variabilities of multiple biological parameters might be observed in patients with systemic conditions and generalized frailty.[21,22] Therefore, it is possible that high cholesterol variability is an epiphenomenon of other systemic conditions that increase cardiovascular or mortality risk. Of note, on the basis of the associations between HDL-C levels and noncardiovascular outcomes, HDL-C is now considered to be more complicated than just being a cardiovascular risk factor.[20] A previous study reported that HDL-C variability also predicted the progression of diabetic nephropathy, including the risk of developing albuminuria.[23] It was recently reported that higher HDL-C variability is associated with incident end-stage renal disease in the general population.[24] Our results clearly indicated that subjects with a high and stable HDL-C are least likely to develop CVD or to die, and that subjects with a low mean and high variability in

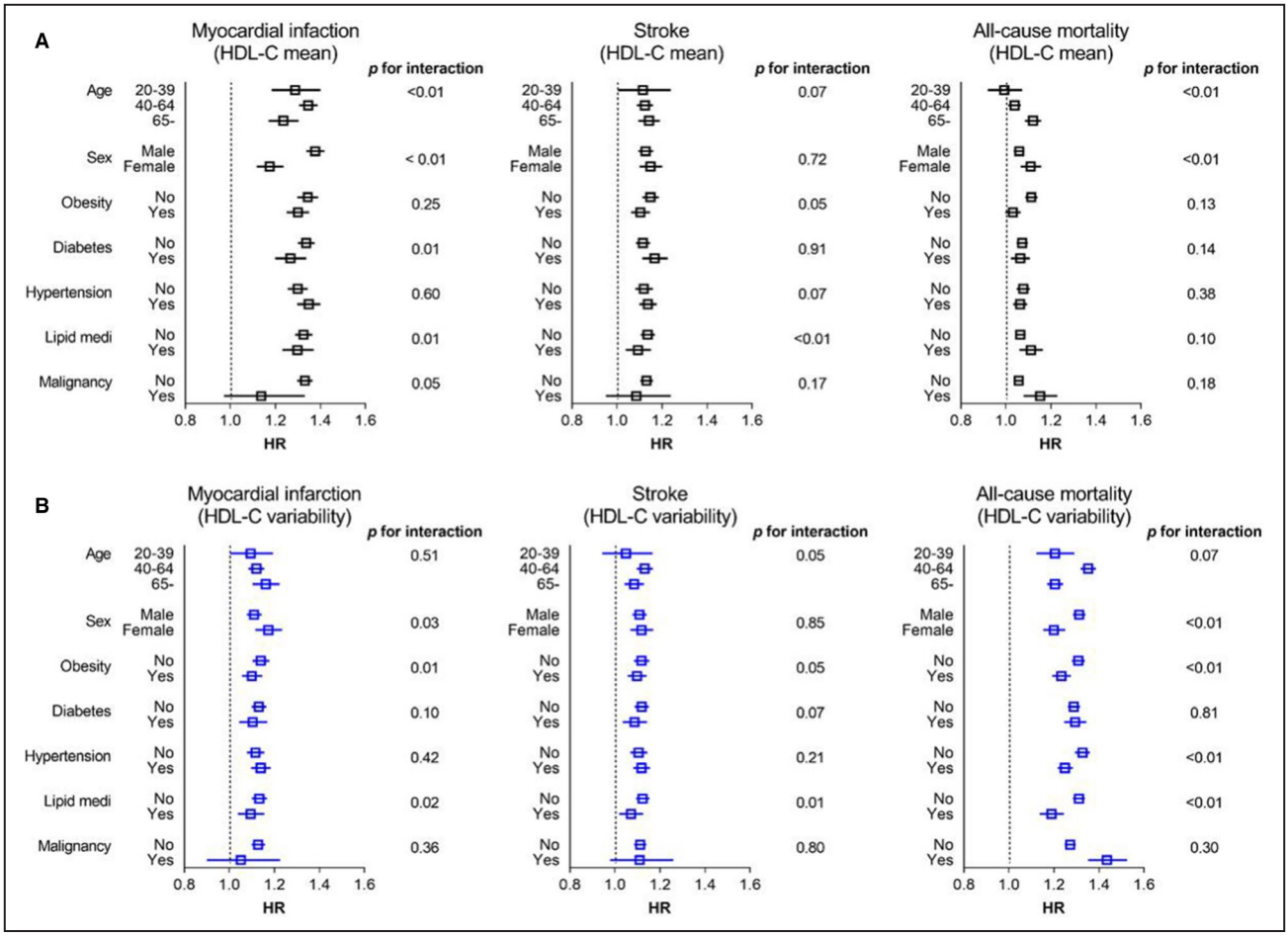

Figure 2. Hazard ratios and 95% CIs for myocardial infarction, stroke, and all-cause mortality in the lowest quartile vs the 3 higher quartiles of mean HDL-C (A) and the highest quartile vs the 3 lower quartiles of HDL-C variability (B) in various subgroups. Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension, and use of lipid-lowering agents.
P values for interaction were analyzed using a likelihood-ratio test. HDL-C indicates high-density lipoprotein cholesterol.

HDL-C had the highest risk of CVD and death. This suggests the important effects of both the absolute value and the variability of HDL-C in terms of the risk of CVD and death in the general population.

In a study of 130 patients with ST-segment–elevation MI, both LDL-C and HDL-C variability were associated with increased risk for major adverse cardiac events. Each 0.01 increase in VIM of LDL-C and HDL-C increased the risk of major adverse cardiac events by 3.5% and 6.8%, respectively.[4] Another study showed that variability in atherogenic lipoprotein levels, such as the SD of LDL-C, was significantly associated with increased risk of coronary atheroma progression and clinical outcomes.[25] However, in contrast with our findings, that study did not find any relationship between HDL-C variability and clinical outcomes. There are several possible explanations for these different results. For example, the study populations differed (Asian versus Western population, general population versus coronary disease population). Other studies also used the SD as a variability index. However, it is known that SD is positively correlated with the mean value, and in the case of HDL-C, mean value and variability might affect outcomes in opposite directions. Therefore, when HDL-C variability was assessed by SD, the effect of HDL-C variability on outcomes might disappear. The VIM and CV are more weakly correlated with the mean value than is SD.[26] We compared CV, VIM, and ARV as indices of HDL-C variability, and the results were largely consistent.

The strengths of our study include the ability to account for multiple possible confounding factors, including lifestyle factors, metabolic factors, and previous history of disease. This is the first study to demonstrate the combined effects of mean HDL-C and its variability on the risk of CVD and all-cause mortality. Moreover, this study population was not composed of diseased patients but was a relatively healthy population. Our study has the strength that

our findings should be applicable to many people. Tsalamandris et al[27] reported that patients with DM had higher HDL-C variability than subjects without DM. Because comorbidities and/or treatments might modulate the changes in lipid parameters during the follow-up, we performed a sensitivity analysis after excluding those with DM, hypertension, or dyslipidemia, which also revealed similar results.

This study did have some limitations. First, excluding participants with fewer than 3 health examinations might have been a source of selection bias. Second, the findings cannot be extrapolated to people of different ethnicities because only the Korean population was included. Third, this was not a prospective study, and the possibility of reverse causation should be considered. To overcome this issue, we performed sensitivity analyses excluding subjects with the occurrence of outcomes within 2 years of follow-up and showed that the results were consistent. Although epidemiologic studies reported an association between low HDL-C and adverse health outcomes, there are genetic studies and randomized clinical trials raising the issue of causality. Neither niacin, fibrate, nor cholesterylester transfer protein inhibitors, agents for increasing HDL-C levels, reduced all-cause mortality, coronary artery disease, or stroke in patients treated with statins.[28] Lifelong low HDL-C levels attributable to heterozygosity for loss-of-function mutations in ABCA1 were not associated with an increased risk of CVD.[29] This finding may be related to low variability of HDL-C attributable to lifelong low HDL-C levels. Future studies should examine whether reducing the variability of HDL-C decreases adverse outcomes and how this reflects the function of HDL.

CONCLUSIONS

In this nationwide population-based cohort study, we observed that low mean and high variability of HDL-C could increase the risk of all-cause mortality, MI, and stroke. Furthermore, we demonstrated an additive effect of mean and variability of HDL-C on CVD outcomes. The data were consistent whether CV, VIM, or ARV was used as an index of variability and in various sensitivity and subgroup analyses.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S7
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. HDL-cholesterol cutoff values in males and females.

	1st quartile	2nd quartile	3rd quartile
Male			
Mean (mg/dL)	45	51	59
CV (%)	7.1	10.8	15.5
VIM (%)	4.2	6.7	10.4
ARV (mg/dL)	4.3	6.5	10.0
Female			
Mean (mg/dL)	52	59	67
CV (%)	7.3	11.1	16.1
VIM (%)	3.3	5.3	8.4
ARV (mg/dL)	5.0	7.7	11.7

ARV, average real variability; CV, coefficient of variation; HDL, high-density lipoprotein; VIM, variability independent of the mean

Table S2. Correlation coefficient between variability of metabolic parameters.

	CV of HDL-C	CV of TG	CV of LDL-C	CV of FBG	CV of BMI
CV of HDL-C	1	-	-	-	-
CV of TG	0.12	1	-	-	-
CV of LDL-C	0.19	0.15	1	-	-
CV of FBG	0.08	0.07	0.11	1	-
CV of BMI	0.06	0.11	0.04	0.05	1

Pearson's correlation coefficient was employed to determine the relationship among parameters. CV, coefficient of variation; HDL-C, high density lipoprotein-cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; FBG, fasting blood glucose; BMI, body mass index

Table S3. The risk of MI, stroke and mortality according to the mean and variability (CV) of HDL-cholesterol: Sensitivity analysis further adjusting for triglyceride levels or triglyceride variability.

	MI		**Stroke**		**Mortality**	
	Model A	Model B	Model A	Model B	Model A	Model B
Mean						
High mean (Q2-4)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Low mean (Q1)	1.31(1.24,1.38)	1.33(1.29,1.36)	1.10(1.05,1.16)	1.13(1.10,1.16)	1.14(1.09,1.19)	1.07(1.05,1.10)
Variability						
Low variability (Q1-3)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
High variability (Q4)	1.12(1.06,1.19)	1.13(1.10,1.16)	1.12(1.07,1.18)	1.11(1.09,1.14)	1.29(1.24,1.35)	1.29(1.26,1.31)
Combination						
High mean/Low Variability	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
High mean /High Variability	1.17(1.09,1.25)	1.16(1.13,1.20)	1.14(1.07,1.21)	1.15(1.11,1.18)	1.28(1.22,1.34)	1.28(1.25,1.31)
Low mean /Low Variability	1.35(1.27,1.44)	1.36(1.32,1.40)	1.12(1.05,1.19)	1.16(1.13,1.20)	1.13(1.07,1.19)	1.07(1.05,1.10)
Low mean /High Variability	1.45(1.33,1.58)	1.47(1.41,1.54)	1.23(1.13,1.33)	1.23(1.18,1.28)	1.51(1.42,1.61)	1.40(1.36,1.45)

Model A: Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension, use of lipid lowering agent and **triglyceride levels**

Model B: Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension, use of lipid lowering agent and **triglyceride variability (CV)**

Table S4. The risk of MI, stroke and mortality according to the mean and variability (VIM) of HDL-cholesterol.

	MI			Stroke			Mortality		
	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)
Mean									
High mean (Q2-4)	17784	0.85	1 (ref.)	20990	1.00	1 (ref.)	36195	1.73	1 (ref.)
Low mean (Q1)	9821	1.42	1.33 (1.29,1.36)	10172	1.47	1.13 (1.10,1.16)	14764	2.13	1.07 (1.05,1.09)
Variability									
Low variability (Q1-3)	17710	0.85	1 (ref.)	20227	0.97	1 (ref.)	32697	1.56	1 (ref.)
High variability (Q4)	9895	1.42	1.26 (1.23,1.30)	10935	1.57	1.14 (1.12,1.17)	18262	2.62	1.25 (1.23,1.28)
Combination									
High mean/Low Variability	13452	0.77	1 (ref.)	15839	0.91	1 (ref.)	27092	1.55	1 (ref.)
High mean /High Variability	4332	1.26	1.24 (1.20,1.28)	5151	1.49	1.16 (1.13,1.20)	9103	2.63	1.24 (1.21,1.27)
Low mean /Low Variability	4258	1.24	1.33 (1.28,1.37)	4388	1.28	1.15 (1.11,1.19)	5605	1.63	0.97 (0.94,1.00)
Low mean /High Variability	5563	1.59	1.45 (1.41,1.50)	5784	1.65	1.19 (1.16,1.23)	9159	2.61	1.41 (1.36,1.45)

* per 1000 person-years

Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension and use of lipid lowering agent. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

Table S5. The risk of MI, stroke and mortality according to the mean and variability (ARV) of HDL-cholesterol.

	MI			Stroke			Mortality		
	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)
Mean									
High mean (Q2-4)	17784	0.85	1 (ref.)	20990	1.00	1 (ref.)	36195	1.73	1 (ref.)
Low mean (Q1)	9821	1.42	1.33 (1.29,1.36)	10172	1.47	1.13 (1.10,1.16)	14764	2.13	1.07 (1.05,1.09)
Variability									
Low variability (Q1-3)	19751	0.95	1 (ref.)	21660	1.04	1 (ref.)	33245	1.59	1 (ref.)
High variability (Q4)	7854	1.13	1.05 (1.02,1.08)	9502	1.37	1.08 (1.06,1.11)	17714	2.54	1.25 (1.23,1.27)
Combination									
High mean/Low Variability	11439	0.77	1 (ref.)	13203	0.89	1 (ref.)	21459	1.44	1 (ref.)
High mean /High Variability	6345	1.04	1.13 (1.10,1.17)	7787	1.28	1.12 (1.09,1.16)	14736	2.41	1.26 (1.24,1.29)
Low mean /Low Variability	8312	1.37	1.37 (1.33,1.41)	8457	1.40	1.17 (1.13,1.20)	11786	1.94	1.11 (1.09,1.14)
Low mean /High Variability	1509	1.75	1.45 (1.37,1.53)	1715	1.99	1.25 (1.19,1.32)	2978	3.44	1.48 (1.42,1.53)

* per 1000 person-years

Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension and use of lipid lowering agent. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

Table S6. The risk of MI, stroke and mortality according to the mean and variability (CV) of HDL-cholesterol (Sensitivity analysis excluding subjects with the occurrence of outcomes within 2 years of follow-up).

	MI			Stroke			Mortality		
	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)
Mean									
High mean (Q2-4)	12769	0.61	1 (ref.)	14171	0.68	1 (ref.)	26080	1.25	1 (ref.)
Low mean (Q1)	6789	0.98	1.28 (1.25,1.32)	6761	0.98	1.12 (1.09,1.16)	10426	1.51	1.04 (1.02,1.07)
Variability									
Low variability (Q1-3)	13472	0.65	1 (ref.)	14094	0.68	1 (ref.)	23366	1.12	1 (ref.)
High variability (Q4)	6086	0.88	1.11 (1.08,1.15)	6838	0.99	1.11 (1.08,1.14)	13140	1.90	1.26 (1.23,1.28)
Combination									
High mean/Low Variability	8666	0.55	1 (ref.)	9403	0.60	1 (ref.)	16601	1.06	1 (ref.)
High mean /High Variability	4103	0.79	1.14 (1.10,1.19)	4768	0.91	1.14 (1.10,1.18)	9479	1.82	1.25 (1.22,1.28)
Low mean /Low Variability	4806	0.92	1.31 (1.27,1.36)	4691	0.90	1.15 (1.11,1.19)	6765	1.30	1.04 (1.01,1.07)
Low mean /High Variability	1983	1.17	1.41 (1.34,1.48)	2070	1.22	1.21 (1.16,1.27)	3661	2.16	1.33 (1.28,1.38)

* per 1000 person-years

Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension and use of lipid lowering agent. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

Table S7. The risk of MI, stroke and mortality according to the mean and variability (CV) of HDL-cholesterol (Sensitivity analysis confined to subjects with 4 health examinations).

	MI			Stroke			Mortality		
	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)	Events (n)	Incidence rate*	HR (95% CI)
Mean									
High mean (Q2-4)	7648	0.73	1 (ref.)	8424	0.80	1 (ref.)	14280	1.36	1 (ref.)
Low mean (Q1)	4006	1.21	1.39 (1.33,1.44)	3597	1.09	1.13 (1.08,1.17)	4992	1.50	1.03 (0.99,1.06)
Variability									
Low variability (Q1-3)	8350	0.79	1 (ref.)	8460	0.80	1 (ref.)	12954	1.22	1 (ref.)
High variability (Q4)	3304	1.04	1.12 (1.07,1.17)	3561	1.12	1.12 (1.08,1.17)	6318	1.99	1.30 (1.26,1.34)
Combination									
High mean/Low Variability	5386	0.67	1 (ref.)	5836	0.72	1 (ref.)	9520	1.18	1 (ref.)
High mean /High Variability	2262	0.93	1.15 (1.09,1.21)	2588	1.06	1.14 (1.09,1.20)	4760	1.95	1.30 (1.25,1.34)
Low mean /Low Variability	2964	1.15	1.41 (1.35,1.48)	2624	1.02	1.15 (1.10,1.21)	3434	1.33	1.03 (0.99,1.07)
Low mean /High Variability	1042	1.42	1.54 (1.44,1.65)	973	1.32	1.24 (1.16,1.33)	1558	2.11	1.36 (1.29,1.44)

* per 1000 person-years

Adjusted for age, sex, body mass index, alcohol drinking, smoking, regular exercise, income status, diabetes mellitus, hypertension and use of lipid lowering agent. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

Figure S1. Flow chart of the study population.