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

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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. KC18ESSI0429). 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 (m²), was measured, and obesity was defined as a BMI ≥25 kg/m².10 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. 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%×(SD/mean)β, where β is the regression coefficient, on the basis of the natural logarithm of the mean. ARV was obtained by calculating the average of the absolute differences between consecutive HDL-C measurements. The number of HDL-C measurements per subject ranged from 3 (n=2862984, 52.7%) to 4 (n=2570114, 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...
Han et al HDL-C and Cardiovascular Outcomes

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

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

|                                | High Mean/Low Variability (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)                       | 687,516 (67.1)                         | 682,528 (67.1)                       | 206,829 (62.0)                       |
| Body mass index, kg/m²         | 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.
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...
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 and outcomes was stronger in nonobese subjects and nonusers of lipid-lowering medications.

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

| 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) | 1,778 | 0.85 | 1 (ref.) | 2,098 | 1.00 | 1 (ref.) | 3,619 | 1.73 | 1 (ref.) |
| | Low mean (Q1) | 982 | 1.42 | 1.33 (1.29, 1.36) | 1,017 | 1.47 | 1.13 (1.10, 1.16) | 1,476 | 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) | 8,750 | 1.26 | 1.13 (1.10, 1.16) | 10,722 | 1.47 | 1.10 (1.07, 1.13) | 18,686 | 2.69 | 1.07 (1.05, 1.09) |
| Combination | High mean/low variability | 11,950 | 0.76 | 1 (ref.) | 13,825 | 0.88 | 1 (ref.) | 22,787 | 1.46 | 1 (ref.) |
| | High mean/high variability | 5,834 | 0.72 | 1.12 (1.09, 1.16) | 7,655 | 1.19 (1.16, 1.22) | 13,408 | 2.56 | 1.07 (1.04, 1.10) |
| | Low mean/low variability | 6,956 | 1.22 | 1.10 (1.07, 1.14) | 8,375 | 1.49 | 1.11 (1.08, 1.14) | 16,596 | 2.90 | 1.05 (1.03, 1.07) |
| | Low mean/high variability | 2,916 | 1.71 | 1.47 (1.41, 1.54) | 3,135 | 1.84 | 1.47 (1.41, 1.54) | 5,278 | 3.08 | 1.47 (1.41, 1.54) |

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.
It is possible that BMI variability may be responsible for the variability in HDL-C. However, we performed correlation analysis and found that the correlation coefficients between HDL-C variability and triglycerides (r = 0.12) or BMI (r = 0.06) were 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." 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. The exact mechanism for the relationship between high variability of HDL-C and an increased risk of CVD is unknown. However, high HDL-C variability could be associated with reduced CVD and mortality, although extremely high HDL-C levels might be paradoxically associated with increased CVD and 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." It is possible that high cholesterol variability is an epiphenomenon of other systemic conditions that increase cardiovascular or mortality risk.
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. 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. 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). 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. 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. Tsalamanidis 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 cholesterylster 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.

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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/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) |
| High 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.

| Mean                  | MI          | Stroke          | Mortality        |
|-----------------------|-------------|-----------------|------------------|
|                       | Events (n)  | Incidence rate* | HR (95% CI)      |
|                       |             |                  |                  |
| High mean (Q2-4)      | 17784       | 0.85            | 1 (ref.)         |
| Low mean (Q1)         | 9821        | 1.42            | 1.33 (1.29,1.36) |
| High mean/Low Variability | 13452   | 0.77            | 1 (ref.)         |
| High mean/High Variability | 4332   | 1.26            | 1.24 (1.20,1.28) |
| Low mean/Low Variability | 4258   | 1.24            | 1.33 (1.28,1.37) |
| Low mean/High Variability | 5563   | 1.59            | 1.45 (1.41,1.50) |
| Variability           |             |                  |                  |
| Low variability (Q1-3)| 17710       | 0.85            | 1 (ref.)         |
| High variability (Q4) | 9895        | 1.42            | 1.26 (1.23,1.30) |
| High mean/Low Variability | 15839  | 0.91            | 1 (ref.)         |
| High mean/High Variability | 5151   | 1.49            | 1.16 (1.13,1.20) |
| Low mean/Low Variability | 4388   | 1.28            | 1.15 (1.11,1.19) |
| Low mean/High Variability | 5784   | 1.65            | 1.19 (1.16,1.23) |
| Combination           |             |                  |                  |
| Low mean/Low Variability | 27092  | 1.55            | 1 (ref.)         |
| Low mean/High Variability | 9103   | 2.63            | 1.24 (1.21,1.27) |
| Low mean/Low Variability | 4388   | 1.63            | 0.97 (0.94,1.00) |
| Low mean/High Variability | 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 Events (n) | Incidence rate* | HR (95% CI) | Stroke Events (n) | Incidence rate* | HR (95% CI) | Mortality 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.

n = 19,459,018
Subjects who underwent health examination in index year (2012 or 2013)

13,826,624 subjects were excluded with less than 3 health examinations

n = 5,632,394
Subjects who underwent ≥ 3 health examinations in preceding 4 years (including index year)

435 subjects with less than 20-yrs-old were excluded

34,810 subjects were excluded with missing data

164,051 subjects were excluded having myocardial infarction or stroke before the index year

n = 5,433,098
Subjects eligible for inclusion

Followed from index year to the date of death or until Dec 31, 2017