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Low Lipid Levels and High Variability are Associated With the Risk of New-Onset Atrial Fibrillation

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Background—While high levels of lipids and lipid variability are established risk factors for atherosclerotic cardiovascular disease, their roles in the development of atrial fibrillation (AF) are unclear, with previous studies suggesting a "cholesterol paradox."

Methods and Results—A nationwide population-based cohort of 3 660 385 adults (mean age 43.4 years) from the Korean National Health Insurance Service database, with ≥3 annual lipid measurements from 2009 to 2012 and without a history of AF or prescription of lipid-lowering medication before 2012, were identified. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides levels were measured, and lipid variability was calculated using variability independent of the mean. The cohort was divided into quartiles by lipid levels and lipid variability and followed up for incident AF. During a median 5.4 years of follow-up, AF was newly diagnosed in 27 581 (0.75%). AF development was inversely associated with high lipid levels (for top versus bottom quartile; total cholesterol, HR 0.78, 95% CI 0.76–0.81; low-density lipoprotein cholesterol, HR 0.81, 95% CI 0.78–0.84; high-density lipoprotein cholesterol, HR 0.94, 95% CI 0.91–0.98; triglycerides, HR 0.88, 95% CI 0.85–0.92). Meanwhile, AF development was associated with high lipid variability (for top versus bottom quartile; total cholesterol, HR 1.09, 95% CI 1.06–1.13; low-density lipoprotein cholesterol, HR 1.12, 95% CI 1.08–1.16; high-density lipoprotein cholesterol, HR 1.08, 95% CI 1.04–1.12; triglycerides, HR 1.05, 95% CI 1.01–1.08). Men showed greater risk reduction with high triglyceride levels and greater risk with high triglyceride variability for incident AF.

Conclusions—Low cholesterol levels and high cholesterol variability were associated with a higher risk of AF development. (*J Am Heart Assoc*. 2019;8:e012771. DOI: 10.1161/JAHA.119.012771.)

Key Words: atrial fibrillation • cholesterol • hypercholesterolemia • lipid • variability

High levels of blood pressure, glucose, cholesterol, and body weight are well-known risk factors for cardiovascular disease. In addition, the variability of these measures is reported to be associated with cardiovascular risk.[1–6] In the case of lipids, variabilities in total cholesterol,[6–8] low-density lipoprotein cholesterol (LDL-C),[9–11] high-density lipoprotein cholesterol (HDL-C),[10,12] and triglycerides[12] are all associated with increased cardiovascular events.

The relationship between cholesterol and incident atrial fibrillation (AF) is less clear. As cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, and chronic kidney disease are also risk factors for AF, it seems that dyslipidemia should also be a risk factor for AF; however, there seems to be a "cholesterol paradox" in AF.[13,14] Hypercholesterolemia has been associated with a lower prevalence of AF.[15] Low levels of LDL-C and total cholesterol[16–20] have been associated with increased AF incidence. Studies have shown an inverse association[13,16,21] or no significant association[17,19–21] between HDL-C and AF, and mostly no association between triglycerides and AF.[16,17,19,20] Meanwhile, compared with the multitude of studies on lipid variability and cardiovascular risk, the association between lipid variability and AF has not yet been studied.

Therefore, we examined the prognostic significance of baseline lipid levels, and investigated whether the variability of lipid parameters is associated with a higher risk of AF in a large population-based cohort.

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Clinical Perspective

What Is New?

- High levels of lipids and lipid variability are established risk factors for atherosclerotic cardiovascular disease, but their roles in atrial fibrillation (AF) development are unclear.
- This study provides strong evidence to support the "cholesterol paradox" that low levels of cholesterols are associated with AF development, and also that high cholesterol variability is associated with AF development.

What Are the Clinical Implications?

- Lipid levels and their variability can provide additional clues for the patient and physician in predicting who will develop AF.
- Whether reducing cholesterol variability can also reduce AF risk requires further investigation.

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Methods

Study Population

The study population was identified from the National Health Insurance Service database, which provides healthcare benefits and regular health check-ups for the total Korean population, and can be used for population-based studies.[8,22–25] Anonymized data are publicly available from the National Health Insurance Sharing Service (nhiss.nhis.or.kr) on request for all researchers whose research protocols have been approved by the Institutional Review Board. Details of the data source are available in Data S1. This study included a retrospective cohort from the general population who underwent government-provided annual health check-ups. Of 12 144 206 subjects (≥20 years) who underwent health examinations in 2012 (index year), those who underwent ≥3 examinations in the prior 4 years (between January 1, 2009 and December 31, 2012) were included (n=4 285 420). Of note, this period was set because the measurement of LDL-C levels in health check-ups started from 2009. Subjects with a history of AF (n=50 955) and subjects on lipid-lowering medications (statin, ezetimibe, fenofibrate) (n=574 080) before the index year were excluded. A total of 3 660 385 subjects were included in the final study population. The study population was followed from the index year until censoring by new-onset AF, death, or until December 31, 2015, whichever came first.

This study was approved by the Institutional Review Board of Seoul National University Hospital (E-1805-112-948), and informed consent was waived.

Data Collection and Definitions

Details of the health examinations are available in Data S1. Baseline characteristics and health examination results were those collected in the index year. All lipid levels showed normal distribution except for triglycerides, which showed a positively skewed distribution. Thus, triglyceride levels were transformed into a logarithmic scale to approximate a bell-shaped normal distribution and are represented by geometric means and 95% CI from back transformation to the original scale. Lipid variability was represented by the variability independent of mean, which is defined to be uncorrelated with mean levels and is calculated as $100 \times SD/mean^{beta}$, where beta is the regression coefficient, on the basis of the natural logarithm of the SD over the natural logarithm of the mean.[8] Two other indices of variability were used in sensitivity analyses: SD, and coefficient of variation. The coefficient of variation was calculated as the ratio of the SD to the mean.

Diseases were defined using the *International Classification of Diseases, Tenth Revision* (*ICD-10*), healthcare usage and medication. The end point was incident AF (*ICD-10* code I48, with ≥1 diagnosis during admission or ≥2 diagnoses at outpatient clinic).[23–25] The definitions for comorbidities are described in Table S1.

Statistical Analysis

Subjects were classified into 4 groups according to baseline lipid level quartiles for the first analysis and 4 groups according to lipid variability quartiles by variability independent of mean for the second analysis. The incidence rates of AF were calculated per 1000 person-years. Cox proportional hazard model was used to calculate hazard ratios (HR) and 95% CI values for the risk of developing AF for the quartiles of lipid levels and variability. Proportional hazards assumption was evaluated graphically using log-log plots, and there was no significant departure from proportionality in hazards over time. Multivariable Cox models were adjusted for age, sex, smoking, alcohol use, regular exercise, income status, presence of hypertension, diabetes mellitus, baseline body mass index, glucose, systolic blood pressure, and estimated glomerular filtration rate. For models where the lipid variability indices were the dependent variables, we further adjusted each model for the corresponding baseline lipid levels. Sex differences were assessed with analyses of *P* for interaction. Sensitivity analyses were performed (1) further adjusting for other comorbidities that can affect lipid levels and AF such as myocardial infarction and other ischemic heart diseases, chronic heart failure, liver disease, and end-stage renal disease, (2) excluding those who started lipid-lowering medication during follow-up, and (3) excluding those with diagnosis of atrial flutter (I48.3, I48.4). Sensitivity analyses for the association between AF and lipid variability were performed using indices of SD and coefficient of variation. Exploratory analyses in subjects on lipid-lowering medication were also performed. Statistical analyses were performed

Table 1. Baseline Characteristics of the Study Population Comparing Those Who Remained AF-Free and Those Who Developed AF

	AF-Free (n=3 632 804)	AF (n=27 581)	*P* Value
Age	43.3±11.2	53.4±12.9	<0.001
Male sex	2 475 158 (68.1)	21 128 (76.6)	<0.001
Comorbidities			
Hypertension	593 627 (16.3)	10 162 (43.8)	<0.001
Diabetes mellitus	172 136 (4.7)	2862 (10.4)	<0.001
Heart failure	5598 (0.2)	359 (1.3)	<0.001
Myocardial infarction	3241 (0.1)	75 (0.3)	<0.001
Ischemic heart disease	43 601 (1.2)	1383 (5.0)	<0.001
Peripheral artery disease	88 599 (2.4)	2003 (7.3)	<0.001
End-stage renal disease	585 (0.02)	27 (0.1)	<0.001
Liver disease	294 581 (8.1)	3914 (14.2)	<0.001
Thyroid disease	62 969 (1.7)	738 (2.7)	<0.001
Lifestyle			
Current smoker	1 147 720 (31.6)	7884 (28.6)	<0.001
Heavy drinker	297 350 (8.2)	2722 (9.9)	<0.001
Regular exercise	762 742 (21.0)	6614 (24.0)	<0.001
Lowest income quintile	570 824 (15.7)	5824 (21.1)	<0.001
Health examination			
Body mass index, kg/m^2	23.6±3.2	24.1±3.1	<0.001
Systolic blood pressure, mm Hg	121±14	125±15	<0.001
Diastolic blood pressure, mm Hg	76±10	78±10	<0.001
Glucose, mg/dL	95±18	100±23	<0.001
Estimated GFR, mL/min	91.7±18.7	87.4±19.2	<0.001
Baseline lipid levels, mg/dL			
TC	193.1±33.0	191.8±33.5	<0.001
LDL-C	112.8±32.5	112.4±30.7	0.012
HDL-C	55.3±15.3	53.5±15.6	<0.001
Triglyceride	109.5 (109.5–109.6)	114.7 (114.0–115.5)	<0.001
Lipid variability (VIM, %)			
TC	16.5±9.0	17.2±9.5	<0.001
LDL-C	19.7±15.9	20.4±16.8	<0.001
HDL-C	7.3±5.1	8.1±5.9	<0.001
Triglyceride	0.309±0.165	0.305±0.163	<0.001

Baseline characteristics are presented as the mean±SD, and n (%) for categorical variables. AF indicates atrial fibrillation; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; VIM, variability independent of mean.

using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA), and *P*<0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics of the Study Population

A total of 3 660 385 subjects (mean age 43.9 years, men 68.2%) were followed up for a median of 5.38 years (interquartile range 0.44 years). Lipid levels were measured 3 (36.4%) or 4 (63.6%) times per subject. AF was newly diagnosed in 27 581 (0.75%), and the incidence of AF was 1.41 per 1000 person-years. Baseline characteristics comparing those who remained AF-free and those who developed AF are described in Table 1. Those who developed AF were older, more likely to be men, obese, had a higher prevalence of comorbidities, higher blood pressure glucose, and lower glomerular filtration rate levels. They smoked less, drank

more, exercised more, and had lower income. Men who developed AF had lower lipid levels, while women who developed AF had higher lipid levels except for lower HDL-C (Table S2). Those who developed AF had generally higher total cholesterol, LDL-C, and HDL-C variability, and lower triglyceride variability (Table S3).

Baseline Lipid Levels and Risk of AF

The study population was classified by lipid quartiles into 4 groups. Median and interquartile ranges of baseline lipid levels are shown in Table S4. In the multivariable adjusted model for the total population, high total cholesterol, LDL-C, HDL-C, and triglyceride levels were associated with a 22%, 19%, 6%, and 12% lower risk of AF, respectively (for top versus bottom quartile; total cholesterol, HR 0.78, 95% CI 0.76–0.81; LDL-C, HR 0.81, 95% CI 0.78–0.84; HDL-C, HR 0.94, 95% CI 0.91–0.98; triglycerides, HR 0.88, 95% CI 0.85–0.92) (Figure 1). The incidence rates and crude HRs are presented in Table S5. There was no significant interaction with sex for the association between total cholesterol, LDL-C, and HDL-C levels with AF development. On the other hand, there was significant sex difference in the association between triglyceride levels and AF (*P* for interaction=0.003). Men showed significantly greater risk reduction for incident AF with high triglyceride levels (HR 0.86, 95% CI 0.82–0.90), compared with women. The association between high triglyceride levels and AF risk was not significant in women.

Lipid Variability and Risk of AF

The study population was classified by lipid variability independent of mean quartiles into 4 groups. In the multivariable adjusted model for the total population, high total cholesterol, LDL-C, HDL-C, and triglyceride variability were associated with a 9%, 12%, 8%, and 5% higher risk of AF, respectively (for top versus bottom quartile; TC, HR 1.09, 95% CI 1.06–1.13; LDL-C, HR 1.12, 95% CI 1.08–1.16; HDL-C, HR 1.08, 95% CI 1.04–1.12; triglycerides, HR 1.05, 95% CI 1.01–1.08) (Figure 2). The incidence rates and crude HRs are presented in Table S6. There was no significant interaction with sex for the association between total cholesterol, LDL-C, and HDL-C variability with AF development. However, there was significant sex difference in the association between triglyceride variability and AF (*P* for interaction=0.004). The association between high triglyceride variability and AF was significant in men (HR 1.07, 95% CI 1.03–1.11), but not in women.

Sensitivity Analyses

Sensitivity analyses further adjusting the main analysis for other comorbidities including myocardial infarction and other ischemic heart diseases, chronic heart failure, liver disease, and end-stage renal disease also showed results consistent with the main analysis (Tables S5 and S6). High levels of all lipids were associated with a lower risk of incident AF, while high variability of all lipids was associated with a higher risk of incident AF in the total population. Sex differences were significant for only triglycerides, and the associations between triglyceride levels or variability were not significant in women. Sensitivity analyses excluding subjects who started lipid-lowering medication during the follow-up period (Table S7) and excluding subjects with a diagnosis of atrial flutter (Table S8) also showed similar results. Sensitivity analyses using SD (Table S9) and coefficient of variation (Table S10) as variability indices also showed that high lipid variability was associated with a higher risk for AF, as in the main analysis.

Exploratory analyses in subjects on lipid-lowering medication showed similar trends for lower risk of AF with higher lipid levels, and a higher risk of AF with high lipid variability, though mostly insignificant (Table S11).

Discussion

In this study, we demonstrated that (1) the "cholesterol paradox" in AF was true for total cholesterol, LDL-C, and HDL-C in both sexes, and for triglycerides in men; (2) higher cholesterol variability of total cholesterol, LDL-C, and HDL-C in both sexes, and of triglycerides in men, was associated with higher risk of incident AF; and (3) sex differences existed for triglycerides: the association between triglyceride levels or variability and AF was not significant in women (Figure 3). To our knowledge, this is the largest cohort study yet on the association between lipid levels and AF, and the first study on the association between lipid variability and AF.

The relationship between lipid levels and the development of AF has been controversial. While hypercholesterolemia is a well-known risk factor for cardiovascular disease, this has not been the case for AF. We found clear inverse associations between total cholesterol and LDL-C with AF development: subjects with the highest quartile of total cholesterol and LDL-C, compared with those with the lowest quartile, showed a risk reduction of 22% and 19% for AF, respectively. Our results are mostly consistent with previous large community-based cohorts (Table 2), in which total cholesterol and LDL-C have generally been inversely associated with AF incidence. The Niigata Preventive Medicine Study,[16] Atherosclerosis Risk in Communities study,[17] Women's Health Study,[18] Swedish Primary Care Cardiovascular Database,[20] and the Chinese Kailuan study[19] found an inverse association between total cholesterol and LDL-C levels with incident AF, and the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium study also found an inverse association between total cholesterol and incident AF.[26] On the other hand, HDL-C has generally shown no
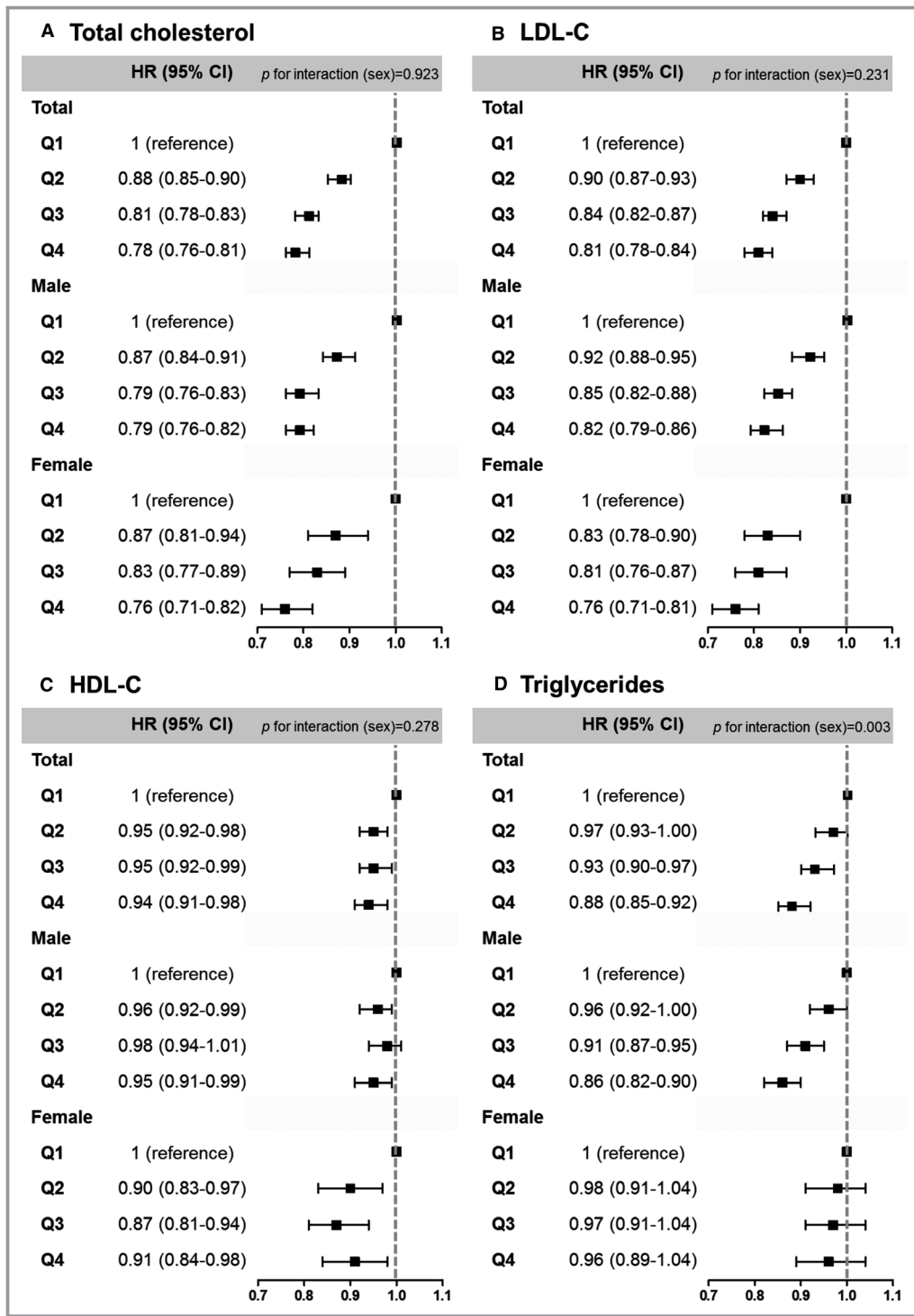
Figure 1. Atrial fibrillation risk by quartiles of baseline lipid levels. **A**, Total cholesterol. **B**, LDL-C. **C**, HDL-C. **D**, Triglycerides. Q1 indicates lowest quartile; Q4, highest quartile; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

association or inverse association with AF, while triglyceride has generally shown no association with AF. Two studies found an inverse association of HDL-C levels with AF (1 only in women),[16,21] while most found no association. We found a small but significant decrease in AF risk with higher HDL-C and triglyceride levels, and this may have been detected because of the higher power, as our study included more subjects than all of the previous cohorts combined.
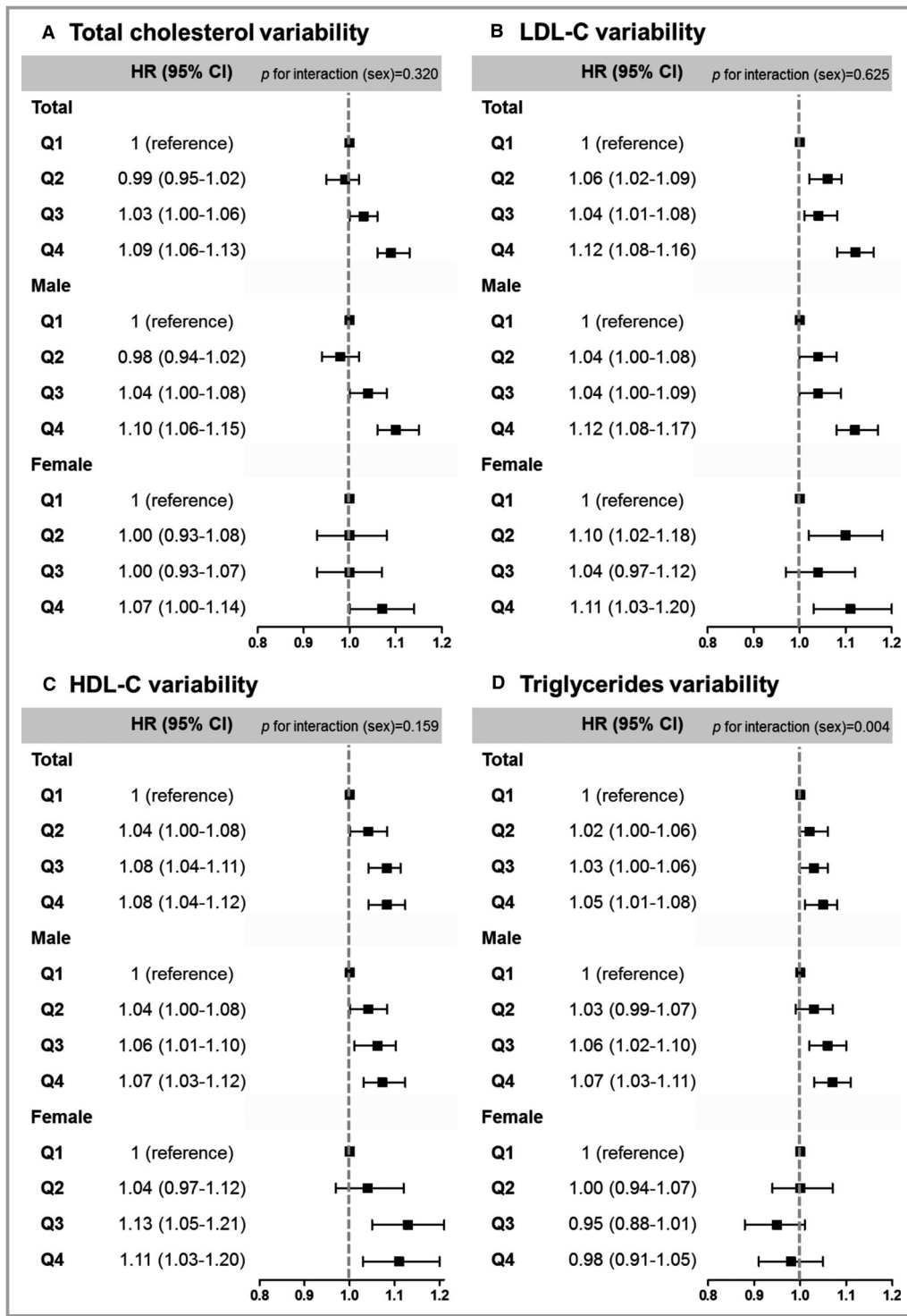
Figure 2. Atrial fibrillation risk by quartiles of lipid variability (variability independent of mean). **A**, Total cholesterol. **B**, LDL-C. **C**, HDL-C. **D**, Triglycerides. Q1 indicates lowest quartile; Q4, highest quartile; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

Meanwhile, 1 study showing diverging results,[21] found an association between high levels of triglyceride with incident AF, while HDL-C showed inverse association and total cholesterol and LDL-C showed no association with AF. However, in the latter study, AF event ascertainment was heterogeneous and there were partly different trends between
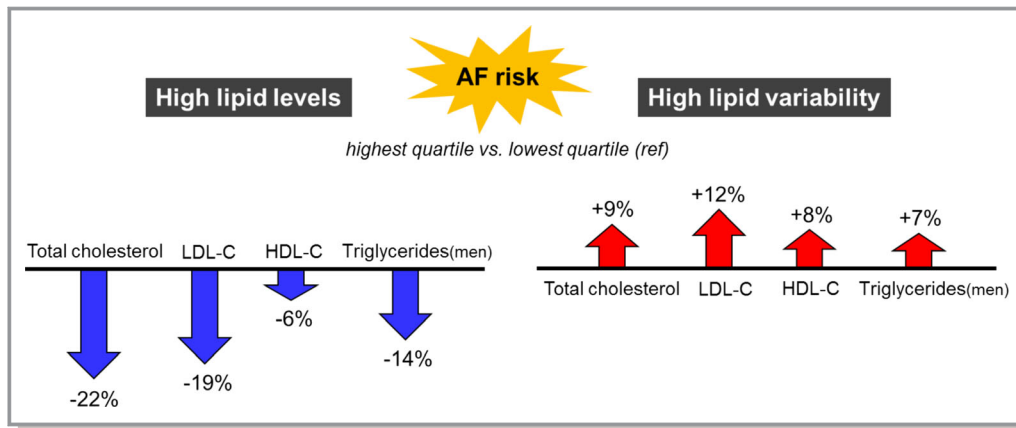
Figure 3. Higher lipid levels were associated with a lower risk of atrial fibrillation, and higher lipid variabilities with a higher risk of atrial fibrillation. AF indicates atrial fibrillation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

lipid levels and AF between the cohorts, which may have contributed to inconsistent results. Another study performed Mendelian randomization analysis in 7 cohorts of European ancestry (n=64 901), and found no significant association between lipid gene scores created from 95 loci significantly associated with lipid phenotypes and incident AF, supporting no direct association between lipid levels and risk of AF.[27] However, each phenotype-specific gene score explained only 1.6% to 6.8% of the variance in cholesterol levels,[28] and did not include later-discovered new loci related to lipid levels. Also, the study population was smaller and heterogeneous methods for measurement of covariates and ascertainment of AF were used.

Recently, interest has increased in the variability of physiological measures, such as blood pressure and body weight, which have been linked to adverse cardiovascular outcomes.[1–5] In the case of lipids, variabilities in total cholesterol,[7,8] LDL-C,[9–11] HDL-C,[10,12] and triglycerides[12] were all associated with increased cardiovascular events in patients with coronary artery disease,[9–11] and in the general population.[7,8] However, the relationship between cholesterol variability and AF development has not yet been studied. A recent study showed that cholesterol variability was significantly associated with coronary atheroma progression and clinical outcomes, providing a plausible mechanism between cholesterol variability and cardiovascular events[29]; though the association between achieved cholesterol levels and atheroma progression was stronger. Similarly, in our study, we found while both cholesterol levels and variability are associated with a higher risk for AF development, the effect of baseline cholesterol levels seem to be stronger than cholesterol variability. Of note, the association between lipid variability and AF was independent of baseline lipid levels in our study.

Sex differences in the association between cholesterol and AF epidemiology were observed in our study, with men showing stronger associations with AF in triglyceride levels and variability, though mostly, the trends were similar in both sexes. Previous studies have also demonstrated sex differences. In the Niigata Preventive Medicine Study,[16] lower HDL-C was associated with a higher incidence of AF in women ≥50 years of age, but not in women <50 years of age or men. In the BiomarCaRE consortium,[26] total cholesterol was inversely associated with incident AF with a greater risk reduction in women (for 1-SD increase; women, HR 0.86, 95% CI 0.81–0.90; men, HR 0.92; 95% CI 0.88–0.97; *P* for interaction=0.023). Hormonal differences may account for sex differences in the link between cholesterol and AF incidence. Premenopausal women tend to have more favorable lipid profiles compared with men, with lower levels of LDL-C, TG, and higher levels of HDL-C, though the differences decrease after menopause. Mechanisms for the sex differences in lipid metabolism are complex, and are mostly attributed to sex hormones, especially estrogen, and may also be related to differences in body fat distribution or insulin sensitivity.[30–32] Also, men show a higher incidence of AF compared with women, though the difference decreases at older age groups.[33] Female patients with AF tend to have more severe symptoms, though they are often treated more conservatively without rhythm management.[34] The biological mechanisms of sex differences in lipid metabolism and AF development warrant further investigation.

Several mechanisms may link cholesterol levels and variability with AF development. First, cholesterol is a main component of the cell membrane, and changes in cholesterol levels can cause changes in membrane properties through effects on membrane permeability and membrane proteins such as ion channels, pumps, and receptors. This can affect

Table 2. Comparison With Previous Large Cohort Studies Examining the Association of Lipid Levels With Atrial Fibrillation

Cohort Study	NHIS (current study)	Niigata	ARIC	WHS	MESA and FHS	BiomarCaRE	SPCCD	Kailuan
Region	Korea	Japan	US	US	US	Europe	Sweden	China
Population	Community-based	Community-based	Community-based	Healthy women	Community-based	Community-based	Hypertensive primary care	Community-based
Size	3 660 385	28 449	13 969	23 738	7142	79 793	51 020	88 785
Female sex, %	31.8	66	55	100	54	51.7	55	21.3
Age, y	43.9 (mean)	59 (mean)	54 (mean)	52.8 (mean)	60 (mean)	49.6 (median)	64 (mean)	50.8 (mean)
Follow-up, y	5.4 (median)	4.5 (mean)	18.7 (median)	16.4 (median)	9.6 (mean)	12.6 (median)	3.5 (mean)	7.1 (mean)
Incident AF	27 581 (0.8%)	265 (0.9%)	1433 (10.3%)	747 (3.0%)	480 (6.7%)	4261 (5.3%)	2389 (4.7%)	328 (0.4%)
Association with AF								
TC	Inverse HR 0.78 (0.76–0.81)*	Inverse HR 0.94 (0.90–0.97)†	Inverse HR 0.89 (0.84–0.95)‡	Inverse HR 0.76 (0.59–0.98)§	None	Inverse RR 0.93 (0.87–0.99)‡	Inverse RR 0.81 (0.72–0.91)‖	Inverse HR 0.60 (0.43–0.83)†
LDL-C	Inverse HR 0.81 (0.78–0.84)*	Inverse HR 0.92 (0.88–0.96)†	Inverse HR 0.90 (0.85–0.96)‡	Inverse HR 0.72 (0.56–0.92)§	None		Inverse RR 0.84 (0.73–0.97)‖	Inverse HR 0.60 (0.43–0.83)
HDL-C	Inverse HR 0.94 (0.91–0.98)	Inverse for women HR 0.78 (0.67–0.93)†	None	None	Inverse HR 0.89 (0.80–0.99)‡		None	None
Triglyceride	Inverse HR 0.88 (0.85–0.92)*	None	None	None	Association HR 1.16 (1.06–1.27)‡		None	None
Subanalysis for sex	Greater risk reduction with high triglycerides in men (P=0.003)	Inverse association with HDL-C in women	N/A	N/A	No interaction with sex	Greater risk reduction with high TC in women (P=0.023)	No interaction with sex	N/A
Lipid-lowering medication	Excluded	Excluded	Adjusted for (no interaction found)	Excluded	Excluded	Not adjusted for	Adjusted for	Excluded in the sensitivity analysis (consistent)

AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BiomarCaRE consortium, Biomarker for Cardiovascular Risk Assessment in Europe; FHS, Framingham Heart Study; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio with 95% CI; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; N/A, not available; NHIS, National Health Insurance Service; RR, relative risk with 95% CI; SPCCD, Swedish Primary Care Cardiovascular Database; TC, total cholesterol; WHS, Women's Health Study.

*For top vs bottom quartile.

†Per 10 mg/dL increase.

‡Per 1-SD increase.

§For top vs bottom quintile.

‖Per 1 mmol/L increase (=39 mL/dL for TC and LDL-C).

electrical gradient and resting potential across the membranes and potentiate the development of arrhythmias.[35] Lower cholesterol levels also increase membrane fluidity and affect membrane function, causing changes in potentials, though how this is related to arrhythmia is not yet clear. Second, the link between cholesterol and AF may be inflammation. Inflammation is associated with the initiation of and perpetuation of AF.[36] Total cholesterol, LDL-C, and HDL-C levels are known to be decreased while triglycerides are increased in inflammation, related to the action of inflammatory cytokines[37]; thus, low levels of cholesterols can reflect the level of inflammation within the host. Also, lipoproteins affect the course of sepsis by binding to bacterial endotoxins and attenuating the harmful excessive inflammatory response[38]; decreased levels of cholesterols can be detrimental to this process. Third, old age or hyperthyroidism is associated with low cholesterol levels, and increased incidence of AF, which may be confounding factors or reflections of the hidden link behind cholesterols and AF. While total cholesterol levels increase with age in the younger population, they decrease in subjects >60 to 70 years old.[14,39] Meanwhile, AF increases with age, especially in the older population.[22] Thyroid hormones upregulate LDL-C receptors, increase cholesterol catabolism and excretion, resulting in a decrease of total and LDL-C, while HDL-C is decreased or unaffected.[40] Subclinical or clinical hyperthyroidism is strongly related to AF development.

Our study suggests that cholesterol variability is a risk factor for AF development, and though speculative, lowering cholesterol variability may be beneficial in the prevention of AF. Statin use has been associated with decreased incidence of AF in a few previous studies.[41,42] This has been attributed to their anti-inflammatory and antioxidant properties, and prevention of atrial structural remodeling,[43,44] and seems independent of their cholesterol-lowering effects.[42,44] Statin therapy also significantly reduces cholesterol variability,[9] which may contribute to protective effects on AF development, though whether this link is valid requires further research. Diet only has been shown to have only a minimal effect on cholesterol levels, while exercise and weight loss have been associated with an increase in HDL-C levels and a decrease in LDL-C and triglyceride levels. How these lifestyle factors affect cholesterol variability are yet unknown. Further studies to examine the mechanisms by which lower cholesterol levels and higher cholesterol variability relate to AF development, and whether the reduction of cholesterol variability can lower AF risk are required.

Several limitations of the current study should be considered. First, AF was identified from a physician's diagnosis of AF in the claims database, and asymptomatic AF incidents without events leading to insurance claims were missed. Discrepancies in recorded and clinical diagnoses for other comorbidities are possible. These are inherent problems of claims databases, which we tried to overcome with refined definitions using combinations of diagnosis codes, hospitalization, or outpatient service usage, medications, and procedure codes, as in previous studies.[22,23] Otherwise, all medical service use of the entire Korean population is included in the database, providing substantial accuracy and completeness of follow-up data. Second, the individuals in the present study may have healthier lifestyles and visit healthcare services more frequently than those who skipped regular check-ups, and there may be some selection bias. Third, we excluded patients on lipid-lowering medication before the index year, including the period of lipid measurements; therefore, we could not examine the effects of lipid-lowering therapy on AF. However, this is also a strength of our study, as we could avoid confounding by medication and examine the independent effects of lipid levels and variability on AF development. Third, as this is a retrospective study, our findings strongly suggest an association between cholesterol levels and variability with incident AF, but this does not mean causation and further studies on the biological mechanisms behind this link are warranted.

Conclusions

In this large nationwide population-based cohort study, lower cholesterol levels and higher cholesterol variability were associated with a higher risk of AF incidence. These findings support the "cholesterol paradox" in AF, and suggest that cholesterol variability is a risk factor for AF development.

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Disclosures

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Details of the data source and health examinations

The National Health Insurance Service (NHIS) provides mandatory coverage for all Korean citizens; thus, its database contains information on demographics, claims data on health care usage, diagnoses, treatments, as well as the health check-up data, and death information data for the entire Korean population, and can be used for population-based studies. The NHIS recommends enrollees to undergo free regular standardized health examinations annually or biennially depending on occupation; office-workers or the self-employed are recommended biennial check-ups while manual workers are recommended annual check-ups. Lipid panels are included as a part of the routine check-ups for all. According to statistics from the Korean Statistical Information Service, the inspection rate was 76.1% in total 17,633,406 subjects scheduled to take the 2015 health examinations.

Standardized health examinations were performed in hospitals certified by the NHIS and subjected to regular quality control. Questionnaires, anthropometric measurements, blood and urine tests, chest x-ray, and dental examinations were included in the health examinations. Blood samples for the measurement of serum glucose and lipid levels were drawn after an overnight fast. Estimated glomerular filtration rate (GFR) was calculated using Modification of Diet in Renal Disease (MDRD) Study equation incorporating age, race, sex, and serum creatinine level. Information on smoking and alcohol consumption, physical activity was obtained by questionnaires. Body mass index (BMI) was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters. Smoking status was checked as non-smoker, ex-smoker, and current smoker, and alcohol consumption was checked as none,

mild (<30g/day), and heavy drinker (≥30g/day). Regular exercise was defined as performing

moderate physical activity more than 30 minutes at least five times per week or strenuous

physical activity more than 20 minutes at least three times per week. Income data was included

in the qualification database, and low income was defined as the lowest 20%.

Table S1. Definitions of comorbidities and outcomes.

	ICD-10 codes	Additional definitions
Comorbidities		
Hypertension	I10-I13, I15	Admission ≥ 1 or outpatient clinic ≥ 2
		Minimum 1 prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker)
Diabetes mellitus	E11-E14	Admission ≥ 1 or outpatient clinic ≥ 2
		Minimum 1 prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors or insulin)
Heart failure	I50	Admission or outpatient clinic ≥ 1
Myocardial infarction	I21, I22	Admission or outpatient clinic ≥ 1
Ischemic heart disease	I20-25	Admission or outpatient clinic ≥ 1
Peripheral artery disease	I70, I73	Admission or outpatient clinic ≥ 1
End-stage renal disease	N18.5, Z49	Dialysis ≥ 2

		Accompanied by procedure claims for hemodialysis (O7011-7020) or peritoneal dialysis (O7017, O7075)
Liver disease	B15, B16, B17, B18, B19, K70, K71, K72, K73, K74, K75, K76, K77	Admission or outpatient clinic ≥ 1
Thyroid disease	E00-E90	Admission or outpatient clinic ≥ 1
Outcomes		
Atrial fibrillation	I48	Admission ≥ 1 or outpatient clinic ≥ 2

Table S2. Baseline characteristics of the study population comparing those who remained AF-free and those who developed AF.

	Male			Female		
	AF-free (n=2,599,431)	AF (n=10,384)	*p*	AF-free (n=1,215,981)	AF (n=2,856)	*p*
Age	43.3±10.9	53.0±12.6	<0.001	43.5±11.9	54.9±13.7	<0.001
Male sex						
Comorbidities						
Hypertension	454,452 (18.4)	7,953 (37.6)	<0.001	139,175 (12.0)	2,209 (34.2)	<0.001
Diabetes mellitus	140,190 (5.7)	2,402 (11.4)	<0.001	31,946 (2.8)	460 (7.1)	<0.001
Heart failure	3,315 (0.1)	228 (1.1)	<0.001	2,283 (0.2)	131 (2.0)	<0.001
Myocardial infarction	2,309 (0.1)	59 (0.3)	<0.001	932 (0.1)	16 (0.3)	<0.001
Peripheral artery disease	51,516 (2.1)	1,383 (6.6)	<0.001	37,083 (2.4)	620 (9.6)	<0.001
End-stage renal disease	492 (0.02)	24 (0.1)	<0.001	93 (0.01)	3 (0.05)	0.0007
Lifestyle						
Current smoker	1,120,564 (45.3)	7,769 (36.8)	<0.001	27,156 (2.4)	115 (1.8)	0.0001
Heavy drinker	284,848 (11.5)	2,674 (12.2)	<0.001	12,502 (1.1)	48 (0.7)	<0.001

Regular exercise	569,421 (23.0)	5,542 (26.2)	<0.001	193,321 (16.7)	1,072 (16.6)	0.8517
Lowest income quintile	289,212 (11.7)	3,786 (17.9)	<0.001	281,612 (24.3)	2,038 (31.6)	<0.001
Health examination						
Body mass index, kg/m^2	24.1±3.0	24.2±3.0	<0.001	22.5±3.2	23.5±3.3	<0.001
Systolic blood pressure, mmHg	123±13	126±14	<0.001	116±14	122±16	<0.001
Diastolic blood pressure, mmHg	78±9	79±10	<0.001	73±9	75±10	<0.001
Glucose, mg/dL	97±20	101±24	<0.001	92±15	96±19	<0.001
GFR, mL/min	90.9±17.4	87.2±18.6	<0.001	93.6±21.2	87.9±21.0	<0.001
Baseline lipid levels (mg/dL)						
TC	194.3±33.0	191.1±33.4	<0.001	190.3±32.9	194.3±33.6	<0.001
LDL-C	113.5±28.6	111.8±28.6	<0.001	109.6±28.0	113.5±28.4	<0.001
HDL-C	52.7±14.8	52.1±15.3	0.0004	61.0±14.8	58.1±15.8	<0.001
TG	123.8 (123.7-123.9)	121.0 (120.1-121.9)	<0.001	84.3 (84.2-84.4)	96.4 (95.2-97.5)	<0.001
Lipid variability (VIM, %)						
TC	16.1±8.5	17.0±9.2	<0.001	17.3±9.8	17.8±10.3	<0.001

LDL-C	19.6±16.3	20.8±17.2	<0.001	19.7±15.1	19.2±15.1	0.0114
HDL-C	7.7±5.3	8.3±6.0	<0.001	6.4±4.5	7.4±5.3	<0.001
TG	0.31±0.17	0.31±0.16	0.0013	0.31±0.17	0.30±0.17	0.0064

AF, atrial fibrillation; GFR, estimated glomerular filtration rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; VIM, variability independent of mean.

Table S3. Lipid variability indexes in the study population comparing those who remained AF-free and those who developed AF.

	Total			Male			Female		
	AF-free (n=3,815,412)	AF (n=13,240)	p	AF-free (n=2,599,431)	AF (n=10,384)	p	AF-free (n=1,215,981)	AF (n=2,856)	p
TC variability									
SD (mg/dL)	16.2±9.2	16.8±9.6	<0.001	16.3±9.1	16.0±8.7	<0.001	16.8±10.0	17.7±10.5	<0.001
CV (%)	8.51±4.62	8.86±4.90	<0.001	8.43±4.39	8.76±4.77	<0.001	8.92±5.07	9.21±5.30	<0.001
VIM (%)	16.5±9.0	17.2±9.5	<0.001	16.1±8.5	17.0±9.2	<0.001	17.3±9.8	17.8±10.3	<0.001
LDL-C variability									
SD (mg/dL)	17.3±9.7	17.8±10.7	0.001	17.5±9.7	17.9±10.5	0.042	16.8±9.7	17.6±11.3	0.028
CV (%)	15.0±10.9	15.5±11.0	<0.001	15.1±11.0	15.6±11.2	<0.001	14.7±10.8	15.1±10.2	<0.001
VIM (%)	19.7±15.9	20.4±16.8	<0.001	19.6±16.3	20.8±17.2	<0.001	19.7±15.1	19.2±15.1	0.011
HDL-C variability									
SD (mg/dL)	7.14±5.14	7.54±5.76	<0.001	6.87±5.00	7.34±5.94	<0.001	7.74±5.33	8.19±5.00	<0.001
CV (%)	12.34±8.95	13.23±9.81	<0.001	12.28±9.27	13.13±9.95	<0.001	12.48±8.24	13.56±9.32	<0.001
VIM (%)	7.25±5.08	8.11±5.86	<0.001	7.67±5.27	8.32±6.01	<0.001	6.36±4.52	7.41±5.28	<0.001

TG variability									
SD (mg/dL)	0.31±0.17	0.31±0.17	0.493	0.31±0.17	0.31±0.17	0.002	0.29±0.16	0.29±0.16	0.636
CV (%)	6.55±3.51	6.45±3.45	<0.001	6.53±3.49	6.46±3.43	0.001	6.58±3.56	6.42±3.53	<0.001
VIM (%)	0.31±0.17	0.30±0.16	<0.001	0.31±0.17	0.30±0.16	0.001	0.31±0.17	0.30±0.17	0.006

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of mean.

Table S4. Median and interquartile ranges of baseline lipid levels.

	Median (Interquartile range)
TC, mg/dL	191 (170-214)
LDL-C, mg/dL	111 (92-132)
HDL-C, mg/dL	54 (45-63)
TG, mg/dL	106 (73-159)

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S5. Incidence rates and atrial fibrillation risk by quartiles of baseline lipid levels.

Lipid	Sex	Quartiles	N	IR[*]	Crude HR (95% CI)	Further adjusted HR[†] (95% CI) [Sensitivity analysis]
TC	Total	Q1	933381	1.46	1 (ref.)	1 (ref.)
		Q2	912141	1.40	0.960 (0.929-0.992)	0.886 (0.857-0.915)
		Q3	885832	1.38	0.947 (0.916-0.979)	0.820 (0.793-0.848)
		Q4	929031	1.38	0.948 (0.917-0.979)	0.804 (0.778-0.832)
	Male	Q1	599599	1.80	1 (ref.)	1 (ref.)
		Q2	615976	1.61	0.897 (0.864-0.931)	0.885 (0.853-0.919)
		Q3	617226	1.49	0.832 (0.801-0.864)	0.809 (0.779-0.841)
		Q4	663485	1.44	0.806 (0.776-0.837)	0.808 (0.777-0.839)
	Female	Q1	333782	0.86	1 (ref.)	1 (ref.)
		Q2	296165	0.97	1.128 (1.051-1.210)	0.883 (0.823-0.948)
		Q3	268606	1.13	1.313 (1.225-1.408)	0.847 (0.789-0.909)
		Q4	265546	1.23	1.431 (1.336-1.532)	0.787 (0.734-0.845)
LDL-C	Total	Q1	898639	1.41	1 (ref.)	1 (ref.)
		Q2	949484	1.38	0.980 (0.947-1.013)	0.907 (0.878-0.938)

		Q3	886374	1.41	1.003 (0.969-1.037)	0.856 (0.827-0.885)
		Q4	925888	1.42	1.011 (0.977-1.045)	0.830 (0.803-0.859)
	Male	Q1	578038	1.72	1 (ref.)	1 (ref.)
		Q2	633618	1.61	0.937 (0.902-0.973)	0.925 (0.891-0.961)
		Q3	619019	1.54	0.897 (0.863-0.932)	0.862 (0.830-0.896)
		Q4	665611	1.48	0.861 (0.828-0.894)	0.842 (0.810-0.876)
	Female	Q1	320601	0.86	1 (ref.)	1 (ref.)
		Q2	315866	0.92	1.077 (1.003-1.156)	0.845 (0.786-0.907)
		Q3	267355	1.12	1.307 (1.218-1.403)	0.825 (0.768-0.887)
		Q4	260277	1.29	1.501 (1.401-1.608)	0.782 (0.729-0.840)
HDL-C	Total	Q1	926960	1.70	1 (ref.)	1 (ref.)
		Q2	901252	1.43	0.841 (0.814-0.868)	0.952 (0.922-0.983)
		Q3	941306	1.32	0.776 (0.751-0.801)	0.959 (0.928-0.992)
		Q4	890867	1.17	0.688 (0.665-0.711)	0.949 (0.916-0.984)
	Male	Q1	783609	1.72	1 (ref.)	1 (ref.)
		Q2	677007	1.52	0.885 (0.854-0.917)	0.961 (0.928-0.996)

		Q3	601535	1.52	0.888 (0.856-0.921)	0.981 (0.945-1.018)
		Q4	434135	1.52	0.889 (0.854-0.926)	0.952 (0.913-0.993)
	Female	Q1	143351	1.62	1 (ref.)	1 (ref.)
		Q2	224245	1.16	0.719 (0.666-0.776)	0.905 (0.838-0.977)
		Q3	339771	0.96	0.593 (0.552-0.638)	0.886 (0.823-0.953)
		Q4	456732	0.83	0.515 (0.480-0.553)	0.920 (0.855-0.99)
TG	Total	Q1	901423	1.16	1 (ref.)	1 (ref.)
		Q2	938491	1.43	1.233 (1.191-1.277)	0.966 (0.933-1.001)
		Q3	910599	1.55	1.344 (1.298-1.391)	0.936 (0.903-0.970)
		Q4	909872	1.49	1.291 (1.247-1.337)	0.891 (0.858-0.925)
	Male	Q1	425839	1.61	1 (ref.)	1 (ref.)
		Q2	596188	1.65	1.026 (0.984-1.07)	0.958 (0.918-0.999)
		Q3	688023	1.62	1.007 (0.967-1.049)	0.917 (0.879-0.957)
		Q4	786236	1.48	0.922 (0.885-0.961)	0.867 (0.831-0.906)
	Female	Q1	475584	0.75	1 (ref.)	1 (ref.)
		Q2	342303	1.03	1.374 (1.289-1.464)	0.975 (0.914-1.04)

Q3	222576	1.35	1.793 (1.678-1.916)	0.975 (0.910-1.045)
Q4	123636	1.54	2.055 (1.905-2.217)	0.967 (0.892-1.048)

* IR: incidence rate per 1,000 person-years.

[†]: further adjustment of main analysis in Figure 1 for myocardial infarction and other ischemic heart diseases, chronic heart failure, liver disease, and end-stage renal disease.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S6. Incidence rates and atrial fibrillation risk by quartiles of lipid variability (variability independent of mean, VIM).

Lipid VIM	Sex	Quartiles	N	IR*	Crude HR (95% CI)	Further adjusted HR† (95% CI) [Sensitivity analysis]
TC	Total	Q1	915096	1.35	1 (ref.)	1 (ref.)
		Q2	915092	1.31	0.974 (0.941-1.008)	0.984 (0.951-1.018)
		Q3	915107	1.39	1.027 (0.993-1.063)	1.025 (0.991-1.06)
		Q4	915090	1.58	1.167 (1.13-1.206)	1.079 (1.044-1.115)
	Male	Q1	638348	1.50	1 (ref.)	1 (ref.)
		Q2	640713	1.46	0.974 (0.936-1.012)	0.980 (0.942-1.019)
		Q3	628560	1.57	1.047 (1.007-1.088)	1.034 (0.995-1.075)
		Q4	588665	1.83	1.224 (1.179-1.271)	1.088 (1.047-1.13)
	Female	Q1	276748	1.01	1 (ref.)	1 (ref.)
		Q2	274379	0.98	0.97 (0.902-1.042)	0.999 (0.930-1.074)
		Q3	286547	1.00	0.982 (0.914-1.054)	0.995 (0.926-1.068)
		Q4	326425	1.12	1.104 (1.032-1.181)	1.054 (0.986-1.128)
LDL-C	Total	Q1	915095	1.36	1 (ref.)	1 (ref.)
		Q2	915094	1.39	1.028 (0.994-1.063)	1.052 (1.016-1.088)

		Q3	915100	1.36	0.999 (0.965-1.033)	1.035 (1-1.073)
		Q4	915096	1.52	1.122 (1.086-1.16)	1.104 (1.063-1.146)
	Male	Q1	640264	1.48	1 (ref.)	1 (ref.)
		Q2	625750	1.53	1.039 (0.999-1.08)	1.040 (1.000-1.081)
		Q3	608668	1.55	1.048 (1.007-1.089)	1.037 (0.996-1.080)
		Q4	621604	1.78	1.205 (1.161-1.251)	1.108 (1.061-1.156)
	Female	Q1	274831	1.08	1 (ref.)	1 (ref.)
		Q2	289344	1.09	1.015 (0.948-1.087)	1.091 (1.018-1.168)
		Q3	306432	0.98	0.906 (0.845-0.971)	1.031 (0.960-1.107)
		Q4	293492	0.98	0.911 (0.85-0.977)	1.095 (1.013-1.184)
HDL-C	Total	Q1	915050	1.15	1 (ref.)	1 (ref.)
		Q2	915251	1.28	1.115 (1.075-1.155)	1.039 (1.002-1.077)
		Q3	914910	1.45	1.26 (1.217-1.305)	1.07 (1.033-1.109)
		Q4	915174	1.74	1.509 (1.459-1.561)	1.069 (1.032-1.108)
	Male	Q1	544709	1.38	1 (ref.)	1 (ref.)
		Q2	606216	1.47	1.064 (1.02-1.109)	1.037 (0.994-1.081)

		Q3	650077	1.58	1.147 (1.102-1.195)	1.053 (1.010-1.097)
		Q4	695284	1.84	1.333 (1.282-1.386)	1.059 (1.017-1.104)
	Female	Q1	370341	0.82	1 (ref.)	1 (ref.)
		Q2	309035	0.93	1.131 (1.055-1.213)	1.040 (0.970-1.116)
		Q3	264833	1.13	1.382 (1.29-1.48)	1.123 (1.047-1.205)
		Q4	219890	1.42	1.738 (1.624-1.861)	1.096 (1.019-1.18)
TG	Total	Q1	915097	1.44	1 (ref.)	1 (ref.)
		Q2	915097	1.42	0.987 (0.954-1.02)	1.023 (0.989-1.057)
		Q3	915095	1.40	0.971 (0.939-1.004)	1.028 (0.994-1.063)
		Q4	915096	1.36	0.946 (0.915-0.978)	1.044 (1.009-1.079)
	Male	Q1	615079	1.61	1 (ref.)	1 (ref.)
		Q2	625761	1.59	0.988 (0.951-1.026)	1.030 (0.991-1.069)
		Q3	627791	1.59	0.983 (0.946-1.021)	1.054 (1.014-1.095)
		Q4	627655	1.54	0.951 (0.916-0.989)	1.065 (1.025-1.107)
	Female	Q1	300018	1.09	1 (ref.)	1 (ref.)
		Q2	289336	1.05	0.965 (0.903-1.033)	1.002 (0.937-1.072)

Q3	287304	0.99	0.913 (0.852-0.977)	0.947 (0.884-1.014)
Q4	287441	0.99	0.909 (0.849-0.973)	0.975 (0.910-1.044)

* IR: incidence rate per 1,000 person-years.

[†] further adjustment of the main analysis in Figure 2 for myocardial infarction and other ischemic heart diseases, chronic heart failure, liver disease, and end-stage renal disease.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S7. Sensitivity analysis excluding subjects who started lipid-lowering medication during follow-up.

Lipid	Quartiles	N	IR[*]	Crude HR (95% CI)	Adjusted HR (95% CI)
Baseline lipid levels					
TC	Q1	877585	1.32	1 (ref.)	1 (ref.)
	Q2	821085	1.25	0.944 (0.910-0.979)	0.875 (0.843-0.907)
	Q3	744413	1.23	0.929 (0.895-0.965)	0.817 (0.787-0.849)
	Q4	657536	1.21	0.920 (0.885-0.956)	0.798 (0.767-0.830)
LDL-C	Q1	830811	1.28	1 (ref.)	1 (ref.)
	Q2	854549	1.23	0.960 (0.925-0.996)	0.886 (0.854-0.919)
	Q3	750210	1.26	0.979 (0.943-1.017)	0.840 (0.809-0.873)
	Q4	665049	1.26	0.980 (0.942-1.019)	0.817 (0.785-0.850)
HDL-C	Q1	743414	1.55	1 (ref.)	1 (ref.)
	Q2	755296	1.27	0.824 (0.794-0.855)	0.927 (0.894-0.963)
	Q3	811781	1.19	0.770 (0.742-0.799)	0.945 (0.910-0.981)
	Q4	790128	1.04	0.670 (0.645-0.697)	0.909 (0.873-0.948)
TG	Q1	835035	1.04	1 (ref.)	1 (ref.)

	Q2	823502	1.28	1.230 (1.183-1.278)	0.980 (0.942-1.019)
	Q3	754526	1.40	1.346 (1.294-1.399)	0.963 (0.925-1.002)
	Q4	687556	1.34	1.288 (1.237-1.340)	0.920 (0.881-0.960)
Lipid variability (VIM)					
TC	Q1	779935	1.20	1 (ref.)	1 (ref.)
	Q2	779491	1.17	0.978 (0.940-1.017)	0.989 (0.950-1.028)
	Q3	776329	1.24	1.035 (0.995-1.076)	1.036 (0.997-1.077)
	Q4	764864	1.42	1.189 (1.144-1.234)	1.119 (1.077-1.162)
LDL-C	Q1	724709	1.21	1 (ref.)	1 (ref.)
	Q2	767143	1.23	1.023 (0.983-1.064)	1.048 (1.007-1.091)
	Q3	797307	1.20	0.994 (0.956-1.035)	1.033 (0.991-1.076)
	Q4	811460	1.37	1.139 (1.096-1.183)	1.130 (1.082-1.180)
HDL-C	Q1	803389	1.03	1 (ref.)	1 (ref.)
	Q2	788580	1.15	1.120 (1.075-1.166)	1.045 (1.004-1.089)
	Q3	770335	1.30	1.261 (1.211-1.312)	1.077 (1.034-1.121)
	Q4	738315	1.58	1.534 (1.476-1.595)	1.102 (1.058-1.148)

				HR (95% CI)	HR (95% CI)
TG	Q1	770076	1.29	1 (ref.)	1 (ref.)
	Q2	773454	1.28	0.988 (0.952-1.027)	1.025 (0.986-1.064)
	Q3	776130	1.25	0.965 (0.928-1.002)	1.022 (0.984-1.062)
	Q4	780959	1.21	0.937 (0.901-0.974)	1.039 (1.000-1.080)

* IR: incidence rate per 1,000 person-years.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S8. Sensitivity analysis excluding subjects with diagnosis of atrial flutter.

Lipid	Quartiles	N	IR*	Crude HR (95% CI)	Adjusted HR (95% CI)
Baseline lipid levels					
TC	Q1	933381	1.46	1 (ref.)	1 (ref.)
	Q2	912141	1.40	0.96 (0.929-0.992)	0.875 (0.846-0.904)
	Q3	885832	1.38	0.946 (0.915-0.978)	0.804 (0.777-0.832)
	Q4	929031	1.38	0.948 (0.917-0.979)	0.782 (0.756-0.809)
LDL-C	Q1	898639	1.41	1 (ref.)	1 (ref.)
	Q2	949484	1.38	0.979 (0.947-1.012)	0.899 (0.869-0.929)
	Q3	886374	1.41	1.002 (0.969-1.037)	0.843 (0.815-0.872)
	Q4	925888	1.42	1.01 (0.977-1.044)	0.810 (0.783-0.838)
HDL-C	Q1	926960	1.70	1 (ref.)	1 (ref.)
	Q2	901252	1.43	0.841 (0.815-0.868)	0.947 (0.917-0.978)
	Q3	941306	1.32	0.776 (0.751-0.801)	0.953 (0.922-0.985)
	Q4	890867	1.17	0.688 (0.665-0.712)	0.941 (0.908-0.976)
TG	Q1	901423	1.16	1 (ref.)	1 (ref.)

	Q2	938491	1.42	1.233 (1.19-1.276)	0.965 (0.931-0.999)
	Q3	910599	1.55	1.344 (1.298-1.391)	0.932 (0.900-0.966)
	Q4	909872	1.49	1.29 (1.246-1.336)	0.883 (0.850-0.917)
Lipid variability (VIM)					
TC	Q1	915096	1.35	1 (ref.)	1 (ref.)
	Q2	915092	1.31	0.973 (0.94-1.007)	0.984 (0.951-1.019)
	Q3	915107	1.39	1.028 (0.993-1.063)	1.029 (0.995-1.065)
	Q4	915090	1.57	1.167 (1.129-1.206)	1.094 (1.058-1.130)
LDL-C	Q1	915095	1.35	1 (ref.)	1 (ref.)
	Q2	915094	1.39	1.028 (0.994-1.063)	1.056 (1.020-1.092)
	Q3	915100	1.35	0.999 (0.965-1.033)	1.043 (1.006-1.080)
	Q4	915096	1.52	1.123 (1.086-1.161)	1.12 (1.079-1.163)
HDL-C	Q1	915050	1.15	1 (ref.)	1 (ref.)
	Q2	915251	1.28	1.115 (1.076-1.156)	1.041 (1.004-1.079)
	Q3	914910	1.45	1.26 (1.217-1.305)	1.074 (1.037-1.113)
	Q4	915174	1.74	1.509 (1.459-1.561)	1.082 (1.044-1.122)

TG	Q1	915097	1.44	1 (ref.)	1 (ref.)
	Q2	915097	1.42	0.985 (0.953-1.018)	1.021 (0.988-1.055)
	Q3	915095	1.40	0.97 (0.938-1.003)	1.028 (0.995-1.063)
	Q4	915096	1.36	0.945 (0.914-0.977)	1.046 (1.012-1.082)

* IR: incidence rate per 1,000 person-years.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S9. Atrial fibrillation risk by quartiles of lipid variability (standard deviation, SD).

Lipid SD	Sex	Quartiles	N	IR*	Crude HR (95% CI)	Adjusted HR (95% CI)	p for trend	p for interaction
TC	Total	Q1	915789	1.33	1 (ref.)	1 (ref.)	<0.001	
		Q2	915267	1.32	0.997 (0.963-1.032)	0.994 (0.961-1.029)		
		Q3	914313	1.41	1.061 (1.026-1.097)	1.038 (1.003-1.074)		
		Q4	915016	1.57	1.187 (1.148-1.226)	1.094 (1.058-1.131)		
	Male	Q1	628012	1.50	1 (ref.)	1 (ref.)	<0.001	0.403
		Q2	635307	1.50	1.004 (0.966-1.044)	1.008 (0.97-1.049)		
		Q3	631284	1.57	1.049 (1.01-1.091)	1.041 (1.002-1.082)		
		Q4	601683	1.77	1.187 (1.143-1.233)	1.106 (1.065-1.15)		
	Female	Q1	287777	0.96	1 (ref.)	1 (ref.)	0.023	
		Q2	279960	0.92	0.956 (0.889-1.029)	0.945 (0.879-1.017)		
		Q3	283029	1.05	1.092 (1.017-1.172)	1.026 (0.956-1.102)		
		Q4	313333	1.19	1.241 (1.161-1.328)	1.056 (0.987-1.131)		
LDL-C	Total	Q1	915851	1.29	1 (ref.)	1 (ref.)	0.098	
		Q2	913332	1.35	1.051 (1.015-1.088)	1.016 (0.981-1.052)		

		Q3	915969	1.41	1.094 (1.058-1.132)	1.007 (0.973-1.042)		
		Q4	915233	1.58	1.225 (1.185-1.267)	1.033 (0.999-1.068)		
	Male	Q1	593007	1.50	1 (ref.)	1 (ref.)	0.092	0.453
		Q2	618495	1.54	1.021 (0.981-1.062)	1.014 (0.975-1.055)		
		Q3	637876	1.58	1.051 (1.011-1.093)	1.019 (0.98-1.059)		
		Q4	646908	1.70	1.133 (1.09-1.177)	1.034 (0.995-1.075)		
	Female	Q1	322844	0.89	1 (ref.)	1 (ref.)	0.697	
		Q2	294837	0.97	1.09 (1.015-1.169)	1.022 (0.953-1.097)		
		Q3	278093	1.02	1.14 (1.062-1.223)	0.969 (0.902-1.04)		
		Q4	268325	1.28	1.431 (1.337-1.531)	1.03 (0.961-1.104)		
HDL-C	Total	Q1	914350	1.36	1 (ref.)	1 (ref.)	<0.001	
		Q2	911888	1.35	0.991 (0.957-1.025)	1.006 (0.972-1.041)		
		Q3	922572	1.38	1.012 (0.978-1.046)	1.021 (0.986-1.056)		
		Q4	911575	1.53	1.124 (1.087-1.161)	1.06 (1.024-1.097)		
	Male	Q1	687668	1.48	1 (ref.)	1 (ref.)	0.068	0.057
		Q2	653119	1.51	1.018 (0.98-1.057)	1.011 (0.974-1.051)		

		Q3	614006	1.56	1.052 (1.013-1.093)	1.009 (0.971-1.049)		
		Q4	541493	1.82	1.228 (1.183-1.276)	1.041 (1.001-1.083)		
	Female	Q1	226682	1.00	1 (ref.)	1 (ref.)	<0.001	
		Q2	258769	0.95	0.95 (0.879-1.027)	0.986 (0.913-1.066)		
		Q3	308566	1.02	1.02 (0.947-1.097)	1.063 (0.988-1.145)		
		Q4	370082	1.11	1.111 (1.036-1.192)	1.119 (1.042-1.202)		
TG	Total	Q1	915096	1.42	1 (ref.)	1 (ref.)	0.023	
		Q2	915096	1.41	0.993 (0.96-1.026)	1.014 (0.981-1.048)		
		Q3	915097	1.40	0.984 (0.952-1.018)	1.01 (0.977-1.044)		
		Q4	915096	1.41	0.992 (0.96-1.026)	1.043 (1.009-1.079)		
	Male	Q1	588005	1.63	1 (ref.)	1 (ref.)	0.001	0.083
		Q2	615892	1.59	0.976 (0.939-1.014)	1.021 (0.982-1.061)		
		Q3	634891	1.56	0.956 (0.92-0.993)	1.028 (0.989-1.068)		
		Q4	657498	1.55	0.95 (0.915-0.987)	1.066 (1.026-1.108)		
	Female	Q1	327091	1.04	1 (ref.)	1 (ref.)	0.196	
		Q2	299204	1.03	0.991 (0.927-1.06)	0.996 (0.931-1.064)		

Q3	280206	1.02	0.988 (0.923-1.057)	0.954 (0.892-1.021)
Q4	257598	1.04	1.004 (0.937-1.076)	0.967 (0.902-1.037)

* IR: incidence rate per 1,000 person-years.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S10. Atrial fibrillation risk by quartiles of lipid variability (coefficient of variation, CV).

Lipid CV	Sex	Quartiles	N	IR*	Crude HR (95% CI)	Adjusted HR (95% CI)
TC	Total	Q1	915084	1.35	1 (ref.)	1 (ref.)
		Q2	915106	1.31	0.974 (0.941-1.008)	0.985 (0.952-1.019)
		Q3	915101	1.39	1.029 (0.995-1.065)	1.031 (0.997-1.066)
		Q4	915094	1.58	1.169 (1.131-1.208)	1.095 (1.06-1.132)
	Male	Q1	638057	1.50	1 (ref.)	1 (ref.)
		Q2	640700	1.46	0.974 (0.937-1.013)	0.981 (0.944-1.02)
		Q3	628707	1.57	1.049 (1.009-1.09)	1.041 (1.001-1.082)
		Q4	588822	1.83	1.225 (1.18-1.272)	1.105 (1.064-1.147)
	Female	Q1	277027	1.01	1 (ref.)	1 (ref.)
		Q2	274406	0.98	0.969 (0.901-1.041)	0.999 (0.929-1.074)
		Q3	286394	1.00	0.983 (0.916-1.056)	0.999 (0.931-1.073)
		Q4	326272	1.12	1.108 (1.036-1.184)	1.069 (0.999-1.143)
LDL-C	Total	Q1	915090	1.32	1 (ref.)	1 (ref.)
		Q2	915100	1.33	1.004 (0.971-1.039)	1.01 (0.976-1.046)

		Q3	915101	1.39	1.052 (1.017-1.089)	1.037 (1.002-1.073)
		Q4	915094	1.58	1.193 (1.154-1.233)	1.06 (1.025-1.097)
	Male	Q1	613598	1.49	1 (ref.)	1 (ref.)
		Q2	622048	1.50	1.004 (0.965-1.044)	1.013 (0.974-1.054)
		Q3	623401	1.57	1.054 (1.014-1.096)	1.046 (1.006-1.088)
		Q4	637239	1.76	1.182 (1.138-1.227)	1.064 (1.024-1.106)
	Female	Q1	301492	0.98	1 (ref.)	1 (ref.)
		Q2	293052	0.98	0.991 (0.924-1.063)	1.002 (0.935-1.075)
		Q3	291700	1.01	1.029 (0.96-1.103)	1.009 (0.941-1.081)
		Q4	277855	1.16	1.181 (1.103-1.264)	1.051 (0.981-1.125)
HDL-C	Total	Q1	915018	1.26	1 (ref.)	1 (ref.)
		Q2	915172	1.30	1.026 (0.99-1.062)	1.014 (0.979-1.05)
		Q3	915141	1.44	1.141 (1.102-1.18)	1.079 (1.043-1.117)
		Q4	915054	1.63	1.288 (1.246-1.332)	1.061 (1.026-1.097)
	Male	Q1	632408	1.43	1 (ref.)	1 (ref.)
		Q2	634759	1.46	1.019 (0.979-1.06)	1.005 (0.966-1.045)

		Q3	623833	1.62	1.134 (1.091-1.179)	1.066 (1.026-1.108)
		Q4	605286	1.83	1.284 (1.236-1.334)	1.042 (1.003-1.082)
	Female	Q1	282610	0.89	1 (ref.)	1 (ref.)
		Q2	280413	0.93	1.046 (0.971-1.127)	1.045 (0.97-1.126)
		Q3	291308	1.06	1.183 (1.101-1.271)	1.125 (1.047-1.209)
		Q4	309768	1.23	1.373 (1.282-1.47)	1.127 (1.052-1.207)
TG	Total	Q1	915096	1.45	1 (ref.)	1 (ref.)
		Q2	915096	1.43	0.986 (0.954-1.019)	1.027 (0.994-1.062)
		Q3	915097	1.40	0.967 (0.935-0.999)	1.035 (1.001-1.07)
		Q4	915096	1.35	0.934 (0.904-0.966)	1.051 (1.017-1.087)
	Male	Q1	623834	1.61	1 (ref.)	1 (ref.)
		Q2	629008	1.60	0.992 (0.955-1.03)	1.034 (0.996-1.074)
		Q3	625595	1.59	0.991 (0.954-1.029)	1.065 (1.025-1.106)
		Q4	617849	1.53	0.953 (0.917-0.99)	1.072 (1.031-1.114)
	Female	Q1	291262	1.11	1 (ref.)	1 (ref.)
		Q2	286088	1.06	0.958 (0.895-1.025)	1.005 (0.939-1.076)

Q3	289502	0.98	0.888 (0.829-0.951)	0.941 (0.878-1.008)
Q4	297247	0.98	0.887 (0.828-0.95)	0.987 (0.922-1.057)

* IR: incidence rate per 1,000 person-years.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table S11. Exploratory analysis in subjects on lipid-lowering medication.

Lipid	Quartiles	N	IR[*]	Crude HR (95% CI)	Adjusted HR (95% CI)
Baseline lipid levels					
TC	Q1	143979	4.41932	1 (ref.)	1 (ref.)
	Q2	141114	3.74543	0.847 (0.806-0.891)	0.966 (0.919-1.017)
	Q3	144798	3.3122	0.749 (0.712-0.789)	0.96 (0.911-1.012)
	Q4	142940	2.54995	0.577 (0.546-0.61)	0.845 (0.796-0.896)
LDL-C	Q1	145404	3.86957	1 (ref.)	1 (ref.)
	Q2	147798	3.43357	0.887 (0.842-0.935)	0.93 (0.882-0.98)
	Q3	135488	3.34559	0.864 (0.819-0.912)	0.925 (0.875-0.977)
	Q4	144141	3.35909	0.868 (0.823-0.915)	0.978 (0.926-1.034)
HDL-C	Q1	144398	4.17836	1 (ref.)	1 (ref.)
	Q2	142052	3.75344	0.898 (0.854-0.945)	0.995 (0.946-1.047)
	Q3	142716	3.39065	0.811 (0.77-0.854)	1.002 (0.95-1.056)
	Q4	143665	2.70162	0.646 (0.612-0.683)	0.912 (0.86-0.966)
TG	Q1	143392	3.74521	1 (ref.)	1 (ref.)

	Q2	143649	3.67637	0.982 (0.932-1.034)	0.932 (0.884-0.982)
	Q3	142893	3.57156	0.954 (0.905-1.005)	0.918 (0.87-0.968)
	Q4	142897	3.02302	0.808 (0.765-0.853)	0.855 (0.807-0.906)
Lipid variability (VIM)					
TC	Q1	143207	3.31379	1 (ref.)	1 (ref.)
	Q2	143209	3.42784	1.034 (0.979-1.093)	1.031 (0.976-1.089)
	Q3	143207	3.61239	1.09 (1.033-1.151)	1.029 (0.975-1.086)
	Q4	143208	3.6642	1.106 (1.048-1.167)	0.96 (0.908-1.014)
LDL-C	Q1	143179	3.18655	1 (ref.)	1 (ref.)
	Q2	143229	3.33278	1.046 (0.989-1.106)	1.018 (0.963-1.077)
	Q3	143216	3.56195	1.118 (1.058-1.181)	1.037 (0.981-1.096)
	Q4	143207	3.93857	1.236 (1.172-1.304)	1.05 (0.993-1.111)
HDL-C	Q1	143208	2.89334	1 (ref.)	1 (ref.)
	Q2	143207	3.35574	1.16 (1.096-1.228)	1.051 (0.992-1.114)
	Q3	143208	3.73329	1.29 (1.221-1.364)	1.046 (0.985-1.111)
	Q4	143208	4.04091	1.397 (1.323-1.476)	1.026 (0.96-1.096)

TG	Q1	143207	3.58941	1 (ref.)	1 (ref.)
	Q2	143208	3.4972	0.974 (0.923-1.027)	1.011 (0.958-1.066)
	Q3	143208	3.49013	0.972 (0.922-1.025)	1.017 (0.964-1.073)
	Q4	143208	3.44069	0.958 (0.908-1.011)	1.02 (0.966-1.076)

* IR: incidence rate per 1,000 person-years.

HR, hazard ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.