Circulation Research

ORIGINAL RESEARCH

Mildly Abnormal Lipid Levels, but Not High Lipid Variability, Are Associated With Increased Risk of Myocardial Infarction and Stroke in "Statin-Naive" Young Population

A Nationwide Cohort Study

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RATIONALE: In young adults, the role of mildly abnormal lipid levels and lipid variability in the risk of atherosclerotic cardiovascular diseases remains uncertain.

OBJECTIVE: To investigate the association of these abnormalities in lipid profiles with the risk of myocardial infarction (MI) and stroke in young population.

METHODS AND RESULTS: From the Korean National Health Insurance Service, a nationwide population-based cohort of 1 934 324 statin-naive adults aged 20 to 39 years, with ≥3 lipid profile measurements and without a history of MI and stroke, were followed-up until the date of MI or stroke, or December 31, 2017. The primary measure of lipid variability was variability independent of the mean. Higher baseline total cholesterol, LDL-C (low-density lipoprotein-cholesterol), and triglycerides and lower HDL-C (high-density lipoprotein-cholesterol) levels were significantly associated with increased MI risk; respective adjusted hazard ratios and 95% CIs comparing the highest versus lowest quartiles were 1.35 (1.20–1.53) for total cholesterol, 1.41 (1.25–1.60) for LDL-C, 1.28 (1.11–1.47) for triglycerides, and 0.82 (0.72–0.94) for HDL-C. Adjusted analyses for deciles of lipid profiles showed that MI risk was significantly elevated among participants with total cholesterol ≥223.4 mg/dL, LDL-C ≥139.5 mg/dL, HDL-C ≤41.8 mg/dL, and triglycerides ≥200.1 mg/dL. The associations between lipid levels and stroke risk were less prominent. Multivariable-adjusted restricted cubic spline analysis demonstrated that the increase in MI risk was not exclusively driven by extreme values of lipid profiles. Similar results were obtained on sensitivity analyses of baseline lipid levels. However, associations between lipid variability and the risk of MI and stroke varied depending on the measure of lipid variability used.

CONCLUSIONS: Mildly abnormal baseline lipid levels were associated with an increased future risk of atherosclerotic cardiovascular disease events, particularly MI, whereas measures of lipid variability were not. Therefore, in young adults, achieving optimal lipid levels could be valuable in the prevention of atherosclerotic cardiovascular disease.

VISUAL OVERVIEW: An online visual overview is available for this article.

Key Words: atherosclerosis ■ cardiovascular disease ■ myocardial infarction ■ triglycerides ■ young adults

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Novelty and Significance

What Is Known?

- Dyslipidemia is accepted as a major and potentially modifiable risk factor for cardiovascular diseases (CVDs).
- Apart from baseline levels of lipid profiles, variabilities of lipid profiles have recently emerged as a potential risk factor for CVDs.
- Although the American College of Cardiology/American Heart Association cholesterol guidelines recommend statin therapy for adults with very high baseline LDL-C (low-density lipoprotein-cholesterol) levels (ie, ≥190 mg/dL), relatively little evidence is available regarding the association between baseline levels of lipid profiles and their variabilities with the risk of myocardial infarction (MI) and stroke in statin-naive young adults aged 20 to 39 years.

What New Information Does This Article Contribute?

- In young patients aged 20 to 39 years, the baseline levels of total cholesterol, LDL-C, and triglyceride are more closely associated with MI than with stroke, with significant differences emerging at their mildly elevated levels (ie, total cholesterol ≥223.4 mg/dL, LDL-C ≥139.5 mg/dL, and triglycerides ≥200.1 mg/dL).
- Higher baseline HDL-C (high-density lipoprotein-cholesterol) levels are associated with a significantly reduced MI risk, even with the mildly elevated HDL-C level (>47.5 mg/dL).
- Variabilities of lipid profiles are not associated with increased risks of MI and stroke.

While the current American College of Cardiology/American Heart Association guidelines recommend the screening for adults to evaluate the risks of atherosclerotic CVDs, relatively little evidence is hitherto available for young adults aged 20 to 39 years regarding the association between lipid profiles and their future CVDs. This study demonstrates that all baseline lipid profiles (ie, total cholesterol, LDL-C, triglycerides, and HDL-C), but not their variabilities, are closely associated with risks of subsequent atherosclerotic CVDs, especially MI, in statin-naive young adults aged 20 to 39 years. Given that even mild abnormalities of lipid profiles can be associated with an increased CVDs risk in this young population, our study highlights the clinical importance of achieving optimal lipid levels to effectively prevent the development of atherosclerotic CVDs in this statin-naive young population. On the contrary, given no association between higher variabilities of lipid profiles and atherosclerotic CVDs, data on the lipid variabilities in statin-naive young adults aged 20 to 39 years should be cautiously interpreted.

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
CVD	cardiovascular disease
HDL-C	high-density lipoprotein-cholesterol
HR	hazard ratio
LDL-C	low-density lipoprotein-cholesterol
MI	myocardial infarction
NHIS	National Health Insurance Service
TC	total cholesterol
VIM	variability independent of the mean

Dyslipidemia is recognized as a major and modifiable contributor to cardiovascular diseases (CVDs) worldwide.[1,2] Specifically, adults with total cholesterol (TC) beyond the optimal level have an increased risk of atherosclerotic CVDs (ASCVDs), such as myocardial infarction (MI) and stroke.[3–5] Recent data suggest that the ASCVD risk reflects the accumulated burden of LDL-C (low-density lipoprotein-cholesterol) exposure over the lifetime,[6] highlighting the value of early identification and interventions to achieve optimal cholesterol levels during young adulthood. Since this approach can help reduce the lifetime risk of ASCVD, the new American College of Cardiology/American Heart Association cholesterol guidelines recommend cholesterol screening in children and adolescents, with a different recommended age for screening depending on the presence or absence of family history of early CVD, significant hypercholesterolemia, or cardiovascular risk factors.[7] For young adults aged 20 to 39 years, however, relatively little evidence is hitherto available to identify individuals at high risk for ASCVD, except for very high LDL-C levels (ie, ≥190 mg/dL).

On the contrary, variability in lipid levels has recently emerged as a predictor of adverse clinical outcomes.[8–10] Lipid-level variability may be causally linked with the ASCVD risk because, theoretically, it can induce fluctuations in the atherosclerotic plaque composition and structure,[11] resulting in plaque instability and rupture, and ultimately, plaque-related clinical events. A recent study suggested that lipid-level variability is also associated with the progression of coronary atheroma and the risk of cardiovascular events,[12] again supporting its causal role in ASCVD.[13,14] However, high lipid-level variability may merely reflect other risk factors or confounders for ASCVD, including unhealthy lifestyle and unrecognized comorbidities. There is a lack of

sufficient data on the effects of lipid-level variability on ASCVD risk in young adults, in whom preventive measures are more important and likely to be more effective.

Therefore, we investigated the association of baseline levels of lipid profiles and their variabilities with the risk of MI and stroke in statin-naive young adults.

METHODS

Data Availability

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified Korean researchers trained in human subject confidentiality protocols may be sent to the Korean National Health Insurance Service (NHIS) at the NHIS' National Health Insurance Data Sharing Service website (http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do).

Study Population

This nationwide population-based cohort study used the database from the NHIS, which includes anonymized health-related information of ≈97% of the Koreans (Please see the Major Resources Table in the Data Supplement).[15] Briefly, all eligible Korean adults, except 3% of the population covered by the Medical Aid program, were recommended to undergo standardized biennial health checkups, which consisted of detailed surveys of demographics, medical histories and health-related behaviors, vital signs and anthropometric measurements, and laboratory tests. We included the data of Korean residents aged 20 to 39 years who had undergone ≥3 health examinations between January 1, 2009 and December 31, 2013.

Variables and Definitions

Information on smoking and alcohol consumption status was obtained using a questionnaire. Participants were also requested to estimate the frequency of physical activity per week and were classified as having physical activity on 0, 1 to 2, 3 to 4, 5 to 6, and 7 days per week. Regular physical activity was defined as reporting ≥5× per week of any type of physical activity. NHIS provided household income data as percentiles without the original continuous data, and the low household income was defined as participants who were at the bottom 20% of the total population. Body mass index was calculated as body weight divided by the square of height (kg/m^2), and obesity was defined as body mass index ≥25 kg/m^2 by the World Health Organization recommendations for Asians. Hypertension was defined by the presence of elevated systolic (≥140 mm Hg) and/or diastolic (≥90 mm Hg) blood pressure, ≥1 claim per year for the *International Classification of Diseases, Tenth Revision* codes for hypertension (I10-11) or ≥1 claim per year for the prescription of antihypertensive medication. Diabetes mellitus was defined by the presence of elevated fasting glucose level (≥126 mg/dL) or ≥1 claim per year for the *International Classification of Diseases, Tenth Revision* codes for diabetes mellitus (E10-14) plus ≥1 claim per year for the prescription of antidiabetic medication. Blood samples for the measurement of lipid profiles and glucose were drawn after an overnight fast. The levels of lipid profile, including TC, LDL-C, HDL-C (high-density lipoprotein-cholesterol), and triglycerides, were measured using an enzymatic method. The quality control of the laboratory tests was conducted in accordance with the procedures of the Korean Association of Laboratory Quality Control.[16] Lipid variability was defined as variability in each component of the lipid profile as measured at least 3× during the health examinations. Variability independent of the mean (VIM) was used as a primary variability index based on previous reports suggesting that VIM may be considered an appropriate measure of visit-to-visit variability,[17,18] which was calculated as 100×SD/mean$^\beta$, where β is the regression coefficient for the natural logarithm of SD on mean. Three different variability indices, coefficient of variation, SD, and average successive variability, were used for sensitivity analyses. The study end points were incident MI and stroke. MI was defined by *International Classification of Diseases, Tenth Revision* codes (I21-22) during hospitalization or these diagnostic codes documented at least twice in the outpatient records. Stroke was defined by *International Classification of Diseases, Tenth Revision* codes (I63-64) for diagnoses made during hospitalization plus claims for brain imaging tests including magnetic resonance imaging and computerized tomography. After the last lipid measurement during the baseline period (2009–2013), the study population was followed-up till the date of MI or stroke or the end of follow-up period (31 December, 2017), whichever was earlier.

Statistical Analysis

Descriptive statistics are presented as means±SD or median (interquartile ranges) for continuous variables and numbers (percentages) for categorical variables. The distributions of baseline levels of and variability in lipid profiles are provided in Online Figure I. The distributions of baseline TC, LDL-C, and HDL-C levels seemed to be approximately normal. However, because the distribution of baseline triglycerides was not normal, this variable was log-transformed, and normal distribution was given thereafter. We, therefore, used the logarithmic transformation of triglycerides as the dependent variable in analyses. For the comparison between groups, unpaired Student *t* test was used for continuous variables, and χ^2 test or Fisher exact test was used for categorical variables, as appropriate. Cox proportional-hazards models were used to assess the association of baseline levels of and variability in lipid profiles with the risk of MI and stroke. Multivariable regression analyses were performed using quartile or decile categories of the baseline levels of and variability in each component of the lipid profiles. All analyses in the present study, including quartile or decile analyses, were prespecified and the cutoff points defining quartiles or deciles are summarized in Online Table I. Hazard ratios (HRs) and 95% CIs were calculated in an unadjusted model, and then recalculated after adjusting for covariates. Nine prespecified potential confounders were included as covariates based on previous reports of factors associated with both exposure (abnormal lipid levels and lipid variability) and outcome (MI and stroke),[19–21] as follows: age, sex, body mass index, physical activity, smoking and alcohol consumption, income level, diabetes mellitus, and hypertension. The interactions between variables were tested. The chronological trend of the risk of developing MI and stroke was expressed as Kaplan-Meier estimates and compared according to the quartiles of baseline levels of or variability in lipid profiles. The log-rank test was used to compare the differences in the study end points. The Cox model with restricted cubic spline regression was constructed to obtain insights into the linearity

of associations between baseline levels of and variability in lipid profiles and the risk of MI and stroke. Two-sided *P* values <0.05 were considered statistically significant. Statistical tests were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Ethics

This study complied with the Declaration of Helsinki and was exempt from review by the Institutional Review Board of our institution (E-1901-112-1005) due to its retrospective data collection from an anonymized database, allowing the maintenance of the participants' confidentiality.

RESULTS

Baseline Characteristics

Of the 4922149 individuals aged 20 to 39 years who underwent health examinations during 2012 and 2013, 1991977 had undergone ≥3 health examinations from 2009 through 2013. To avoid the confounding effects of statins on lipid levels and variability, we excluded 32705 subjects who were on statins during the baseline period (ie, 2009–2013). We also excluded 15373 individuals with missing values for lipid profiles and covariates. To minimize the reverse causality bias resulting from changes in lipid levels or variability caused by preexisting MI or stroke, we excluded 9575 subjects with a history of MI or stroke, resulting in a final study population of 1934324 individuals (Figure 1). To minimize the risk of bias related to statin use, participants who received statins during follow-up (n=129945) were treated as censored cases. Table 1 summarizes the characteristics of the study population. The characteristics of individuals excluded from the study due to the frequency of health examinations not fulfilling the prespecified criteria (ie, individuals having health examinations <3) are presented in Online Table II.

Association of Baseline Levels of Lipid Profiles With MI and Stroke

During a median follow-up of 5.2 years (interquartile range, 4.7–5.5), 2295 and 1593 incidences of MI (0.24%) and stroke (0.16%) occurred, respectively. The risk of MI and stroke according to the baseline lipid levels is summarized in Table 2. The risk of MI was significantly higher in the highest quartile of baseline TC level versus the lowest one (adjusted HR, 1.354 [95% CI, 1.199–1.529]), while the difference in stroke risk was insignificant between the same groups. The associations of the baseline LDL-C level with the risk of study end points were similar to those of TC, with a greater difference in the risk of MI (adjusted HR for highest versus lowest quartiles, 1.414 [95% CI, 1.253–1.596]) and with an insignificant difference in that of stroke. The risk of MI and stroke was significantly lower in the highest quartile of baseline HDL-C level versus the lowest one (adjusted HR, 0.821 [95% CI, 0.720–0.936]), with statistical significance being observed from the second quartile for MI and the fourth quartile for stroke. The highest quartile of baseline triglycerides level demonstrated significantly higher risks of MI (adjusted HR, 1.278 [95% CI, 1.105–1.478]) and stroke (adjusted HR, 1.259 [95% CI, 1.055–1.502]), respectively, than the lowest one. Unadjusted Kaplan-Meier plots are illustrated in Online Figure II. The results were essentially similar when the analysis was performed for individuals excluded from the study (Online Table III).

We also estimated the HRs of MI and stroke at decile cutoff points along the baseline levels of lipid profiles, with the first decile being the reference group (Figure 2). There was significantly higher multivariable-adjusted HR of MI only in the10th decile (D10) of baseline levels of TC (≥223.4 mg/dL), LDL-C (≥139.5 mg/dL), and triglycerides (≥200.1 mg/dL) and no significant associations in the second to ninth deciles, compared with the lowest decile as the reference group. However, the HR of MI decreased gradually and reached statistical significance from the second decile (D2) of the baseline HDL-C level (>42 mg/dL). Similar patterns were observed for the risk of stroke, but its magnitude of increase was smaller than that for MI. The HR of stroke increased in a stepwise fashion without statistical significance even in the 10th decile (D10) of baseline levels of TC, LDL-C, and triglycerides. However,

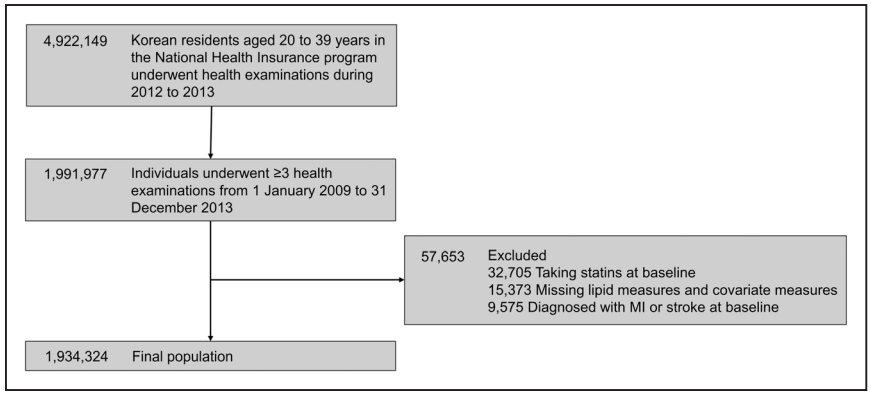

Figure 1. Flow diagram of the study population.
MI indicates myocardial infarction.

Table 1. Baseline Characteristics of Study Participants

Characteristics	Total (n=1 934 324)
Age, y	32.23±4.32
Male	1 347 208 (69.7)
Urban residence	804 428 (41.6)
BMI, m/kg^2	23.5±3.6
WC, cm	79.1±9.8
Systolic BP, mm Hg	118.6±12.7
Diastolic BP, mm Hg	74.7±9.1
Hypertension	134 991 (7.0)
Diabetes mellitus	33 513 (1.7)
Atrial fibrillation	380 (0.02)
CHF	1126 (0.1)
ESRD	4552 (0.2)
Regular physical activity*	338 796 (17.5)
Smoking	
Never	944 497 (48.8)
Former	261 347 (13.5)
Current	728 480 (37.7)
Alcohol consumption	
0 g/d	628 748 (32.5)
1–30 g/d	1 132 786 (58.6)
>30 g/d	172 790 (8.9)
Low income level	183 648 (9.5)
Hemoglobin	14.7±1.5
Glucose	91.5±14.8
Mean TC	188.1±33.4
TC variability	
VIM, %	16.5±9.3
SD, mg/dL	15.8±9.4
CV, %	8.5±4.8
ASV, mg/dL	19.1±12.4
Mean LDL-C	108±3.8
LDL-C variability	
VIM, %	23.2±40.2
SD, mg/dL	17.0±30.7
CV, %	15.4±12.3
ASV, mg/dL	20.0±28.6
Mean HDL-C	56.2±15.4
HDL-C variability	
VIM, %	6.9±5.1
SD, mg/dL	6.9±9.8
CV, %	11.8±8.3
ASV, mg/dL	8.2±10.4
Mean triglycerides†	104.3 (104.2–104.4)
Triglycerides variability	
VIM, %†	1.4 (1.4–1.4)
SD, mg/dL†	1.4 (1.4–1.4)
CV, %†	858.2 (853.7–862.7)
ASV, mg/dL†	1.5 (1.5–1.5)
Creatinine	0.9±0.3
GFR	99.6±52.4

Values given as number (percentage), mean±SD, or median (interquartile range) unless otherwise indicated. ASV indicates average successive variability; BMI, body mass index; BP, blood pressure; CHF, congestive heart failure; CV, coefficient of variation; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; VIM, variability independent of the mean; and WC, waist circumference.

*Regular physical activity was defined as any type of physical activity for ≥5× per week.

†Geometric mean.

the HR of stroke decreased gradually with increasing deciles of HDL-C levels, with a statistically significant difference in D10.

When restricted cubic spline regression was used to explore the linear or nonlinear relationships between baseline levels of lipid profiles and the study end points (Figure 3), MI risk increased progressively with increasing TC, LDL-C, and triglyceride levels, without being driven by the individuals with extremely high values of TC, LDL-C, triglyceride. A progressive increase in MI risk was found with decreasing HDL-C level. The association of TC and LDL-C with stroke risk was relatively weak compared with that seen in MI, while the levels of HDL-C and triglyceride showed approximately linear associations with stroke risk.

Association of VIM in Lipid Profiles With MI and Stroke

The risks of MI and stroke according to VIM in the lipid profiles are summarized in Table 3. The risks of MI and stroke did not differ between the highest quartile of VIM of TC versus the lowest one. The risk of MI was significantly lower in the second and highest quartiles of VIM of LDL-C than the lowest one (adjusted HR, 0.874 [95% CI 0.780–0.978] and 0.823 [0.732–0.926], respectively), but there were no significant inter-group differences in the risk of stroke. The risk of MI was significantly higher in the third and highest quartiles of VIM of HDL-C than those in the lowest one; however, stroke risk was similar between the quartiles. The risk of MI was significantly lower in the second quartile of VIM of triglycerides than the lowest one, but there were no significant differences in stroke risk between these quartiles. The corresponding Kaplan-Meier curves are presented in Online Figure III.

Figure 4 illustrates the HRs of study end points at decile cutoff points along the VIM values of lipid profiles. The risk of MI significantly decreased with increasing

Table 2. Adjusted Risk of Myocardial Infarction and Stroke According to Baseline Values of Lipid Profiles

	Myocardial Infarction				Stroke			
	Events	PY	IR	HR (95% CI)	Events	PY	IR	HR (95% CI)
Mean baseline TC								
Q1	449	2464508	0.182	1 (ref.)	341	2464783	0.138	1 (ref)
Q2	498	2489827	0.200	0.985 (0.867–1.120)	331	2490243	0.132	0.832 (0.715–0.968)
Q3	541	2428411	0.223	0.988 (0.870–1.122)	397	2428749	0.163	0.899 (0.776–1.042)
Q4	807	2295986	0.351	1.354 (1.199–1.529)	524	2296302	0.228	1.062 (0.920–1.227)
P_{trend}				<0.001				0.134
Mean baseline LDL-C								
Q1	444	2458259	0.181	1 (ref)	357	2458530	0.145	1 (ref)
Q2	520	2466749	0.211	1.077 (0.949–1.223)	336	2467152	0.136	0.845 (0.728–0.981)
Q3	531	2436187	0.218	1.005 (0.884–1.142)	379	2436554	0.155	0.854 (0.738–0.990)
Q4	800	2317536	0.345	1.414 (1.253–1.596)	521	2317842	0.225	1.073 (0.932–1.235)
P_{trend}				<0.001				0.180
Mean baseline HDL-C								
Q1	805	2379596	0.338	1 (ref)	519	2380008	0.218	1 (ref)
Q2	603	2399027	0.251	0.871 (0.783–0.969)	422	2399402	0.176	0.936 (0.822–1.066)
Q3	467	2448812	0.191	0.765 (0.679–0.862)	368	2449111	0.150	0.910 (0.791–1.046)
Q4	420	2451296	0.171	0.821 (0.720–0.936)	284	2451556	0.116	0.808 (0.688–0.948)
P_{trend}				<0.001				0.011
Mean baseline triglycerides								
Q1	365	2472964	0.148	1 (ref)	253	2473186	0.102	1 (ref)
Q2	515	2463163	0.209	1.125 (0.981–1.292)	331	2463554	0.134	1.080 (0.913–1.277)
Q3	558	2429522	0.230	0.999 (0.866–1.153)	447	2429866	0.184	1.210 (1.022–1.432)
Q4	857	2313083	0.371	1.278 (1.105–1.478)	562	2313471	0.243	1.259 (1.055–1.502)
P_{trend}				0.003				0.006

P_{trend} indicates P for linear trend across quartiles. Hazard ratios were calculated by Cox regression analysis after adjustment for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension. HDL-C indicates high-density lipoprotein-cholesterol; HR, hazard ratio; IR, incidence rate per 1000 person-years; LDL-C, low-density lipoprotein-cholesterol; PY, person-years; and TC, total cholesterol

deciles of VIM of LDL-C, whereas it was not significantly associated with those of TC, HDL-C, and triglycerides. The risk of stroke was not different across the deciles of VIM of each lipid component. In restricted cubic splines, there was no clear positive or negative association between VIM in lipid profiles and the risks of MI and stroke, except that MI risk increased gradually as VIM of HDL-C increased (Figure 5).

Interactions Between Major Variables

When we tested the interactions between baseline levels of lipid profiles using quartile analysis, the highest rates for MI occurred when both LDL-C and triglycerides were in the highest quartile, with the next highest rates for either LDL-C or triglycerides alone in the highest quartile, with the lowest rates when LDL-C and triglycerides were both in lower quartiles. Similar interactions were found between TC and triglycerides. The highest MI risk was noted among individuals in lower quartiles of HDL-C and the highest quartile of LDL-C or TC, followed by those in both lower quartiles of HDL-C and LDL-C or TC, with the lowest risk for those in the highest quartile of HDL-C and lower quartiles of LDL-C or TC. The highest rates for stroke occurred when HDL-C was in lower quartiles and TC was in the highest quartile, with intermediate rates when HDL-C and TC were both in lower quartiles or both in the highest quartile, with the lowest rates when HDL-C was in the highest quartile and TC was in lower quartiles (Online Table IV). Regarding VIM of lipid profiles, a significant interaction was only observed between HDL-C and triglycerides for the risk of MI (Online Table V).

When we tested the interactions between VIM of lipid profiles and their baseline levels using quartile analysis, there were no significant interactions between the variables for the risks of MI and stroke (Online Table VI).

Subgroup Analysis

Higher baseline levels of TC, LDL-C, and triglyceride, and lower levels of HDL-C were associated with generally higher risks of MI and stroke across the subgroups of age, sex, the presence or absence of diabetes mellitus

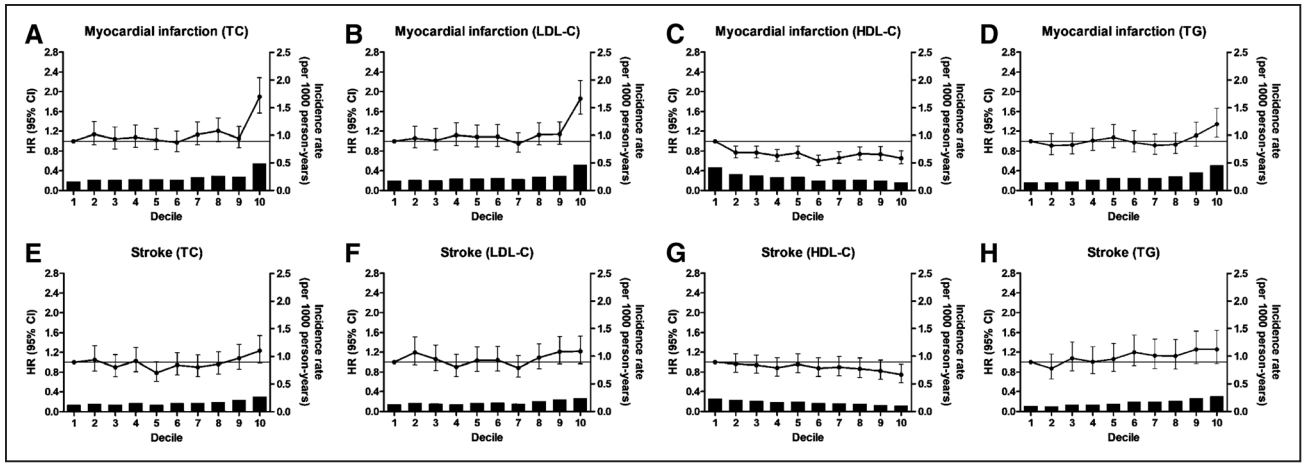

Figure 2. Incidence rates and hazard ratios for myocardial infarction and stroke by deciles of baseline levels of lipid profiles.
Solid lines indicate the hazard ratios, and error bars indicate the 95% CIs. Hazard ratios were calculated by Cox regression analysis after adjusting for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension. Colored bars indicate the incidence rates per 1000 person-years. HDL-C indicates high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; and TG, triglycerides.

and hypertension, and smoking and alcohol drinking status (Online Figure IV). Significant interactions were present for TC and LDL-C levels with sex, smoking status, and diabetes mellitus. Specifically, the association of baseline levels of TC and LDL-C with the risk of MI was significantly greater in men than women, current smoker than nonsmoker or ex-smoker, and diabetic than nondiabetic individuals. The association between triglycerides and MI risk was significantly more pronounced in men, smoker, and nonheavy drinker. Regarding HDL-C, there were no significant interactions by these subgroups. When the same analyses were repeated for stroke risk, there were no statistically significant interactions with baseline levels of lipid profiles across the subgroups. The association between VIM of lipid profiles and the risk of MI and stroke across the subgroups are provided in Online Figure V.

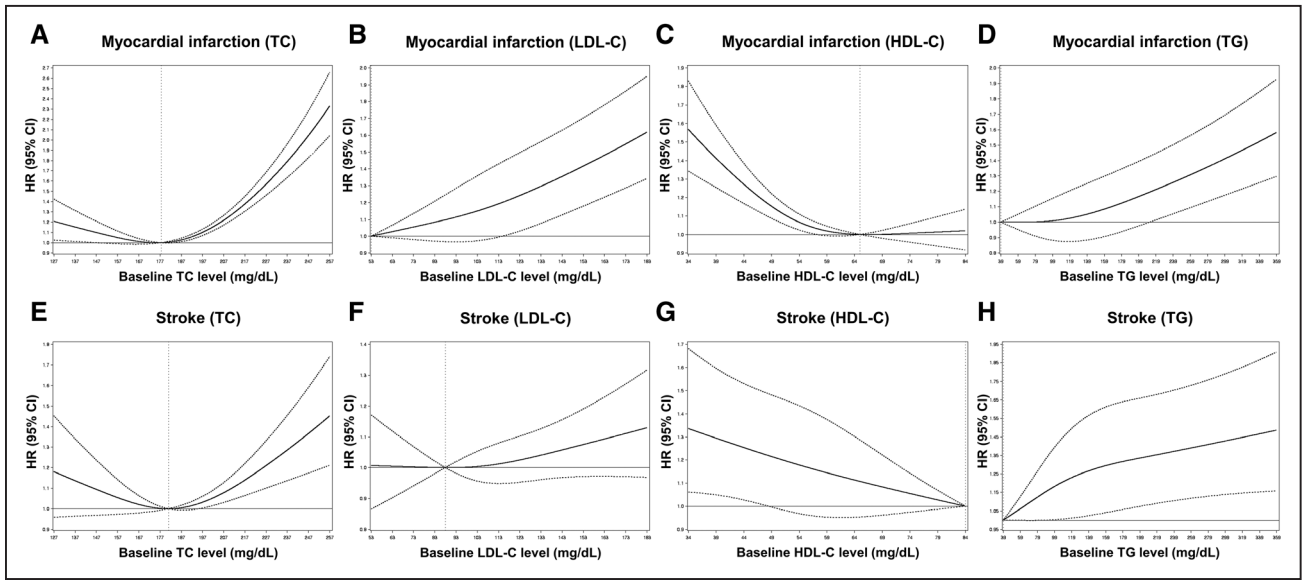

Figure 3. Restricted cubic spline regression model of the hazard of myocardial infarction and stroke by baseline values of lipid profiles.
Note the direct associations of total cholesterol (TC), LDL-C (low-density lipoprotein-cholesterol), and triglyceride levels with myocardial infarction (MI) risk, and an inverse association between HDL-C level and MI risk (**A**–**D**). There are relatively weak associations of TC and LDL-C levels with stroke risk (**E** and **F**), while there is an approximately linear negative relationship between HDL-C level and stroke risk (**G**), and a positive relationship between triglycerides and stroke risk (**H**). Nonlinear associations are modelled using restricted cubic splines with 95% CIs. Hazard ratios were calculated by Cox regression analysis after adjusting for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension. The values of TC, LDL-C, HDL-C, and triglyceride with the lowest hazard ratio (HR) were chosen as reference. Knots were placed at the 10, 50, and 90th percentiles of the distribution of baseline values of lipid profiles. Solid blue line presents hazard ratio, and dashed black line presents 95% CI. TG indicates triglycerides.

Table 3. Adjusted Risk of Myocardial Infarction and Stroke According to Variability in Lipid Profiles

	Myocardial Infarction				Stroke			
	Events	PY	IR	HR (95% CI)	Events	PY	IR	HR (95% CI)
VIM of TC								
Q1	551	2409675	0.229	1 (ref)	406	2409946	0.168	1 (ref)
Q2	565	2431026	0.232	0.998 (0.888–1.122)	397	2431327	0.163	0.953 (0.830–1.094)
Q3	600	2430049	0.247	1.062 (0.946–1.192)	402	2430473	0.165	0.970 (0.845–1.113)
Q4	579	2407981	0.240	1.062 (0.945–1.194)	388	2408330	0.161	0.965 (0.839–1.109)
P_{trend}				0.194				0.686
VIM of LDL-C								
Q1	655	2371436	0.276	1 (ref)	437	2371702	0.184	1 (ref)
Q2	564	2426959	0.232	0.874 (0.780–0.978)	407	2427259	0.168	0.957 (0.836–1.095)
Q3	573	2445275	0.234	0.925 (0.826–1.035)	361	2445743	0.148	0.895 (0.778–1.029)
Q4	503	2435061	0.207	0.823 (0.732–0.926)	388	2435371	0.159	0.987 (0.859–1.133)
P_{trend}				0.005				0.609
VIM of HDL-C								
Q1	462	2429656	0.190	1 (ref)	353	2429950	0.145	1 (ref)
Q2	497	2436858	0.204	0.968 (0.853–1.100)	392	2437042	0.161	1.008 (0.873–1.165)
Q3	628	2423900	0.259	1.136 (1.006–1.283)	395	2424396	0.163	0.951 (0.822–1.099)
Q4	708	2388318	0.296	1.167 (1.035–1.316)	453	2388687	0.190	1.001 (0.868–1.155)
P_{trend}				0.001				0.838
VIM of triglycerides								
Q1	579	2397904	0.241	1 (ref)	413	2398198	0.172	1 (ref)
Q2	495	2425322	0.204	0.833 (0.739–0.939)	406	2425508	0.167	0.967 (0.843–1.109)
Q3	601	2430377	0.247	1.014 (0.904–1.136)	400	2430781	0.165	0.966 (0.842–1.109)
Q4	620	2425128	0.256	1.070 (0.955–1.199)	374	2425591	0.154	0.937 (0.815–1.079)
P_{trend}				0.032				0.390

P_{trend} indicates P for linear trend across quartiles.Hazard ratios were calculated by Cox regression analysis after adjustment for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension. HDL-C indicates high-density lipoprotein-cholesterol; IR, incidence rate per 1000 person-years; LDL-C, low-density lipoprotein-cholesterol; PY, person-years; TC, total cholesterol; and VIM, variability independent of mean.

Sensitivity Analysis

When we repeated all analyses using other indices for lipid variability as a sensitivity analysis, the results remained virtually unchanged, but the significant association between higher VIM of LDL-C with lower MI risk was lost when other indices were applied (Online Table VII). Specifically, higher coefficient of variation of LDL-C was not associated with decreased risk of MI, and higher SD and average successive variability was significantly associated with increased risk of MI, which was opposite to the result using VIM. In additional sensitivity analysis, we reanalyzed the data after excluding subjects with chronic serious illnesses, including cancer, liver cirrhosis, and chronic obstructive pulmonary disease, and found similar results (Online Table VIII). The results were basically unchanged when we further excluded individuals with congestive heart failure and atrial fibrillation (Online Table IX). When analysis was performed in individuals with baseline LDL-C levels ≥140 but <190 mg/dL, MI risk was significantly higher in the highest quartile of baseline LDL-C level versus the lowest one (HR, 1.329 [95% CI, 1.173–1.506]; Online Table X). In a final sensitivity analysis, we used the average value of all available LDL-C values and found that the higher average value of LDL-C was significantly associated with the risk of MI (HR for highest versus lowest quartile, 1.329 [95% CI, 1.178–1.500]; Online Table XI).

DISCUSSION

The main findings of the present study conducted in statin-naive adults aged 20 to 39 years are as follows: (1) the baseline levels of TC, LDL-C, and triglycerides were more closely associated with MI than with stroke, with significant differences emerging at the levels of TC ≥223.4 mg/dL, LDL-C ≥139.5 mg/dL, and triglycerides ≥200.1 mg/dL; (2) higher baseline HDL-C level was significantly associated with reduced MI risks, even with the mildly elevated level of HDL-C (> 47.5 mg/dL) demonstrating statistical significance; and (3) variabilities in lipid traits were not consistently associated with increased risks of MI and stroke.

Recognizing cumulative effects of high lipid values over a lifespan can help reduce the lifetime risk of ASCVDs. The European dyslipidemia guideline also suggests that the approach of lifetime risk may be useful in younger adults,

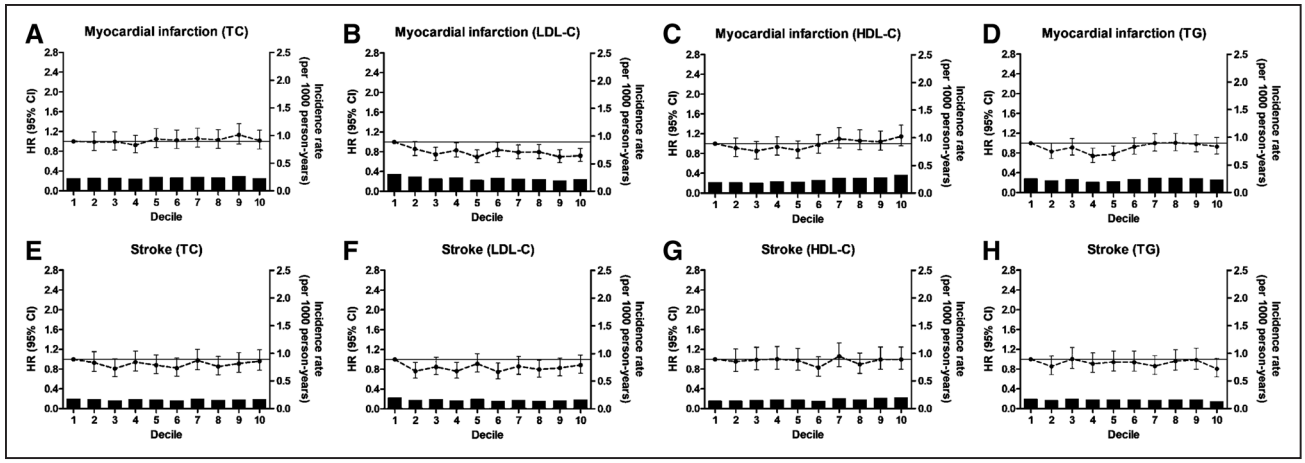

Figure 4. Incidence rates and hazard ratios for myocardial infarction and stroke by deciles of variability in lipid profiles.
Dashed lines indicate the hazard ratios, and error bars indicate the 95% CIs. Hazard ratios were adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension. Colored bars indicate the incidence rates per 1000 person-years. HDL-C indicates high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; and TG, triglycerides.

which produces greater risk figures for younger adults due to their longer exposure times.[22] However, because of a paucity of evidence, there are fewer recommendations for young adults aged 20 to 39 years, except for statin therapy for those with severe primary hypercholesterolemia, defined as LDL-C ≥190 mg/dL. A previous study demonstrated that young adults experiencing prolonged exposure to higher TC levels had a substantially increased lifetime risk of coronary heart disease, supporting the important role of cholesterol screening in the younger population.[23] Our study demonstrated that the risk of incident MI was significantly higher in young adults with TC, LDL-C, and triglycerides levels above D10 (≈>220 mg/dL, >140 mg/dL, and >200 mg/dL, respectively). Notably, multivariable-adjusted restricted cubic spline analysis demonstrated that the increase in MI risk was not exclusively driven by the individuals with extremely increased or decreased values of lipid profiles. Furthermore, in a sensitivity analysis excluding individuals with baseline LDL-C levels ≥190 mg/dL, there was a significant association

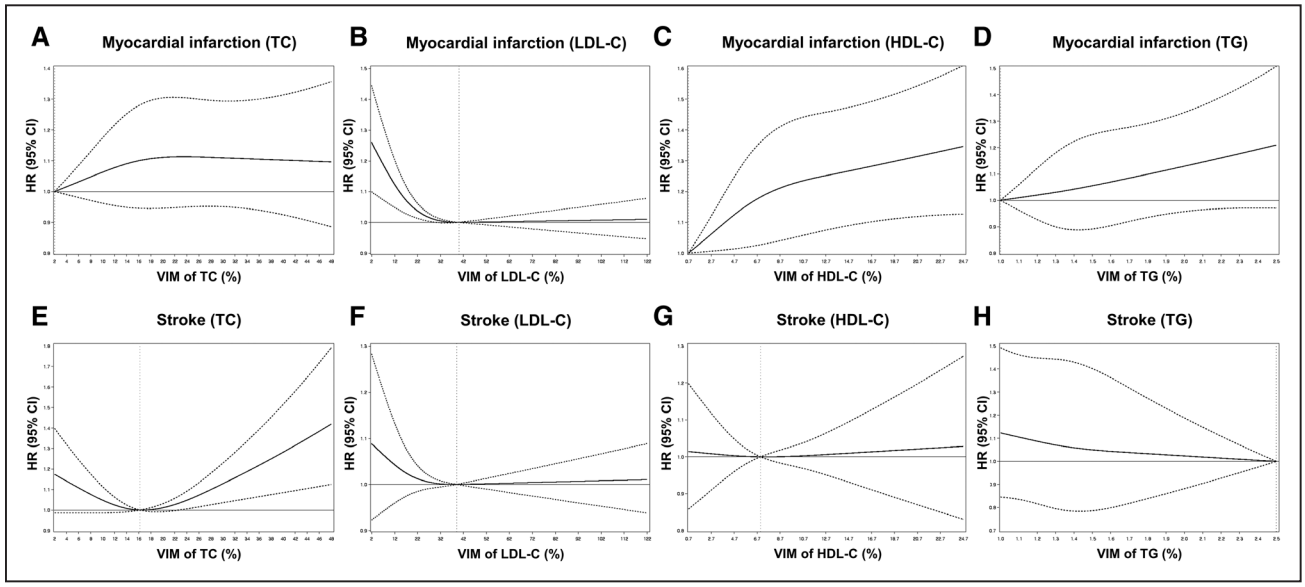

Figure 5. Restricted cubic spline regression model of the hazard of myocardial infarction (MI) and stroke by variability in lipid profiles.
Higher VIM in 4 lipid profiles are not consistently associated with increased risks of MI and stroke, except for a positive association between VIM of HDL-C and MI risk. Nonlinear associations are modelled using restricted cubic splines with 95% CIs. Hazard ratios were adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension. The values of total cholesterol (TC), LDL-C (low-density lipoprotein-cholesterol), HDL-C (high-density lipoprotein-cholesterol), and triglyceride with the lowest hazard ratio (HR) were chosen as reference. Knots were placed at the 10, 50, and 90th percentiles of the distribution of variability independent of the mean (VIM) of lipid profiles. Solid blue line presents hazard ratio, and dashed black line presents 95% CI. TG indicates triglycerides.

between higher LDL-C and MI risk. These findings imply that young adults with relatively mildly elevated cholesterol levels might have increased subsequent ASCVD risk, which is in line with a previous study showing a significant association between cumulative exposure to moderate hyperlipidemia in early adulthood and future risk of coronary heart disease.[24] Thus, it might be suggested that young adults with moderate LDL-C elevation could be considered candidates for statin therapy.

The associations of baseline TC and LDL-C values with increased risk of stroke were not as clear as those of MI in our study. Although this finding is in line with previous studies suggesting the stronger association of lipid levels with MI than with stroke,[25,26] this relatively weak association with stroke may be mostly due to the lower incidence of stroke during the limited follow-up period in our study. This can also be explained by a relatively greater contribution of hypertension and cardio-embolic origins to stroke than to MI.[27]

While only the highest deciles of TC and LDL-C were associated with a dramatic increase in MI risk, even a small increase in baseline HDL-C level above D2 (>42 mg/dL) was significantly associated with reduced MI risk (Figure 3). This finding corroborates a recent study suggesting that young adults who experience their first MI are likely to have low HDL-C levels rather than high LDL-C levels.[28] This study also highlights the need of continued research investigating the impact of HDL-C on cardiovascular prognosis of young adults to improve the current guidelines for this population, since a large proportion of young patients with MI would not have met the current guideline-based thresholds to initiate statin therapy in the primary prevention setting, where LDL-C values and/or 10-year ASCVD risk are mainly focused on. Another study demonstrated that nonoptimal HDL-C level, defined as HDL-C <60 mg/dL, was observed in ≈72.8% of young adults before 35 years of age, and the exposure to low HDL-C level during young adulthood was independently associated with coronary calcium persisting into the middle ages.[29] Therefore, in a young population, HDL-C might be a better biomarker of risk than the conventional LDL-C. However, considering that HDL-C is not a causal factor of ASCVDs, but a risk variable confounded by lifestyle characteristics like physical activity, obesity, and smoking,[30] our observation may emphasize the importance of lifestyle modifications to reduce the risk of MI in young adults. Our study also demonstrated the strong association between baseline triglycerides levels and MI, again emphasizing healthy lifestyle behaviors in reducing the risk of ASCVDs. Furthermore, we found that the combination of low HDL-C and high TC or LDL-C, as well as the combination of high triglycerides and high TC or LDL-C exerted synergistic adverse effects on the risk of MI, suggesting that lifestyle modifications should be made wherever possible, when any disordered lipid profile is detected in young adults.

Higher variabilities in all lipid profiles were not consistently associated with increased risk of MI or stroke. This result is contradictory to those of previous studies reporting a positive association between lipid variability and cardiovascular events.[10,12,31] One hypothesis explaining this positive association is that cholesterol variability hinders the efflux of lipid from an atheroma and contributes to ongoing plaque progression and its vulnerability to rupture.[12,32] Although this hypothesis seems plausible, it is still possible that high lipid-level variability is merely a reflection of nonadherence to medications and/or comorbid conditions that act as important confounders in determining the clinical outcomes rather than being truly representative of a causality. In the present study, subjects who were on statin therapy at baseline were excluded and those during follow-up were censored, precluding the possible confounding effects of statin use on lipid variability. Hence, associations between lipid variability and ASCVD risk previously reported could be explained by adherence to statin therapy.[10] Based on this observation, our study suggests the use of measures of lipid variability in predicting future MI and stroke events may not be appropriate due to the issue of possible confounding by statin therapy. However, statin use as a potential confounder cannot explain the opposite direction of effect for HDL-C and triglycerides (ie, their positive associations with MI) observed in our study. Therefore, another possibility is that high lipid variability may reflect lifestyle changes, where adding together positive and negative changes can lead to errors in the estimation of the true effect. Although several lifestyle behaviors at baseline, including smoking, alcohol consumption, and physical activity, were adjusted as confounders, these and other lifestyle changes over time could contribute to the degree of lipid variability. Future studies are needed to resolve this issue.

Strengths and Limitations

This was a large-scale study that included only statin-naive young adults aged 20 to 39 years, in whom few specific recommendations were proposed according to the American College of Cardiology/American Heart Association cholesterol guidelines, except for recommending statin therapy for those having LDL-C ≥190 mg/dL.[7] Therefore, this study can provide unprecedented evidence regarding lipid management recommendations in this age group.

Several limitations should be acknowledged in this study. First, our study cannot prove causality, although we excluded subjects with previous MI or stroke at baseline to mitigate the potential concerns of reverse causality. Second, since the study population was derived from a single country, the findings may not be generalizable to different ethnicities. Third, lipid variability may be influenced by a number of factors. To minimize this confounding effect, we employed 3 alternative indices of lipid variability as sensitivity analyses and found no significant association

of lipid-level variabilities with MI and stroke events. Fourth, although we chose VIM as a main measure of lipid variability based on previous evidence supporting its use in assessing visit-to-visit variability,[17,18] VIM is a more complicated measure than others. Furthermore, it is still difficult to recommend one measure of lipid variability against another, from both research and clinical standpoints. Fifth, data on the study end points, that is, MI or stroke, were obtained only from administrative data, which can be misleading. However, the accuracy of NHIS claims data for the diagnosis of MI and stroke has been previously validated.[33,34] Sixth, it should be acknowledged that the finding that cholesterol levels are significantly associated with subsequent risk of cardiovascular morbidity and mortality was first reported in the Framingham study and has been extensively validated. Despite this limited novelty, our study was the largest, involving only statin-naive young adults aged 20 to 39 years, in whom relatively few recommendations were proposed in the cholesterol guideline available.[7] Therefore, this study can provide unprecedented evidence regarding lipid management in this age group. Seventh, there were significant differences between the included and excluded populations. Specifically, excluded individuals appeared to be healthier in terms of many of the baseline variables collected, such as better lifestyle behaviors (smoking and alcohol consumption) and lipid profiles (Online Table II). More importantly, there were only 30% women included in this study, the proportion of which was much lower than expected. This could lead to a relatively small sample size of women, which may result in mostly nonsignificant associations between baseline lipid levels and risk of MI and stroke for women in our subgroup analyses (Online Figure IV). One possible explanation for this relatively small proportion of women in our study is that pregnant or postpartum women may not undergo regular health checkups. Although similar health checkups might be performed in the clinic for antenatal care, these data are not incorporated into the Korean National Health Insurance Service database. Given that our study population included individuals aged 20 to 39 years, which is compatible with the childbearing age, it is possible that, compared with men, a relatively large proportion of women was excluded according to the criterion of individuals having health examinations ≥3. Indeed, when we assessed the proportion of excluded women and men due to not fulfilling this prespecified criterion, 67.2% of the women (1 353 447 of 2 013 553) and 54.2% of the men (1 576 725 of 2 908 596) were excluded, respectively, supporting our speculation. Our results should thus be cautiously interpreted, as the differences in baseline characteristics between included and excluded individuals, particularly, the proportion of sex, may limit the generalizability of the study. Eighth, we should take into account the potential presence of residual, which is inherently difficult to avoid in observational studies. Finally, given the very low rates of MI and stroke in our study, the clinical value of measuring lipid profiles in young adults aged 20 to 39 years, and its cost-effectiveness is questionable. Since the low event rates were partly due to the short follow-up time (5.2 years) in this study, further studies with longer follow-up are needed to estimate the lifetime risk of MI and stroke among young adults when abnormal lipid profiles are not appropriately managed, and assess whether the screening of lipid abnormalities in young adults has prognostic value in predicting future risk of MI and stroke and is of cost-effectiveness or not. Similarly, future studies are also warranted to determine whether lipid variability can provide incremental prognostic information beyond baseline levels of lipid profiles.

Conclusions

In statin-naive young adults, higher baseline TC, LDL-C, and triglycerides levels and lower HDL-C levels were associated with higher risks of subsequent ASCVD, especially MI. Given that relatively mild abnormalities of lipid profiles portended an increased risk of MI in young adults, our study highlights the importance of achieving optimal lipid levels to prevent ASCVDs in young populations. In contrast, higher variabilities in all lipid profiles were not significantly associated with heightened risks of MI or stroke in statin-naive young adults. Therefore, data on the lipid variabilities should be interpreted with caution.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Online Figures I–V
Online Tables I–XI
Major Resource Table

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