ORIGINAL RESEARCH

Effect of Moderately but Persistently Elevated Lipid Levels on Risks of Stroke and Myocardial Infarction in Young Korean Adults

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BACKGROUND: Identifying predictive markers for future atherosclerotic cardiovascular diseases may be helpful to motivate young adults to promote healthy lifestyle. We sought to determine the association between persistently elevated low-density lipoprotein-cholesterol (LDL-C) and/or triglyceride levels and the atherosclerotic cardiovascular diseases risks in young adults.

METHODS AND RESULTS: We conducted a nationwide population-based cohort study of 1 887 853 statin-naive adults aged 20 to 39 years, with LDL-C <190 mg/dL, using the Korean National Health Insurance Service database. Persistently elevated LDL-C and triglyceride levels were defined by ≥3 measurements of ≥160 and ≥175 mg/dL, respectively. The primary outcome was a composite of stroke and myocardial infarction. Among the study population, 11 121 (0.59%) and 167 373 (8.87%) had persistently elevated LDL-C and triglycerides, respectively. During a median follow-up of 5.2 years, 2170 and 1537 incidences of stroke (0.16%) and myocardial infarction (0.23%) occurred. Persistently elevated LDL-C levels were significantly associated with increased risks of the primary outcome, with an adjusted hazard ratio (HR) of 1.396 (95% CI, 1.005–1.940). This association was independent of high-density lipoprotein cholesterol. Persistently elevated triglycerides were significantly associated with increased risks of the primary outcome (HR, 1.120; 95% CI, 1.015–1.236), but attenuated after adjustment for high-density lipoprotein cholesterol.

CONCLUSIONS: Persistently elevated LDL-C and triglyceride levels were associated with atherosclerotic cardiovascular diseases risk in young Korean adults without severe hypercholesterolemia. These lipid abnormalities should be considered risk factors in young adults since their effects on lifetime atherosclerotic cardiovascular diseases risk may become more pronounced over the life course.

Key Words: myocardial infarction ■ persistently elevated lipid levels ■ stroke ■ young adults

D yslipidemia is a major risk factor for cardiovascular diseases that is readily modifiable through lifestyle changes and/or pharmacotherapy.[1,2] As the risk of atherosclerotic cardiovascular diseases (ASCVDs) such as stroke and myocardial infarction (MI) reflects the lifetime cumulative burden of dyslipidemia,[3] its mounting effects are expected to be a greater burden to younger individuals than to older individuals. In fact, the risk factor for stroke most frequently reported among adults aged 15 to 49 years is dyslipidemia, while in the elderly population, the most frequent risk factor is hypertension.[4] In adults aged 18 to 44 years

CLINICAL PERSPECTIVE

What Is New?

- Among participants with low-density lipoprotein-cholesterol (LDL-C) <190 mg/dL, the proportion of individuals with persistently elevated LDL-C was small (0.59%), but the proportion of those with persistently elevated triglycerides was substantial (8.87%).
- Persistently elevated LDL-C of 160 to 189 mg/dL were independently and significantly associated with increased risks of the composite of myocardial infarction and stroke and the individual outcome of stroke, regardless of adjustment for high-density lipoprotein cholesterol.
- Persistently elevated triglycerides ≥175 mg/dL were independently and significantly associated with increased risk of composite of myocardial infarction and stroke and the individual outcome of myocardial infarction, but this association was attenuated after adjustment for high-density lipoprotein cholesterol.

What Are the Clinical Implications?

- Persistently elevated LDL-C and triglycerides need to be considered as risk factors in young adults in whom their effects on lifetime atherosclerotic cardiovascular disease risk may become more pronounced because of the longer exposure times.
- Our results contribute to further identifying high-risk individuals for atherosclerotic cardiovascular diseases, particularly among individuals without severe abnormalities in their initial lipid levels and thus without the current indications for statin therapy.
- Given that repeated measurements of lipid profiles are used in routine clinical practice, the assessment of persistently elevated LDL-C and triglycerides could be readily applied by clinicians to improve prediction of future atherosclerotic cardiovascular disease events.

Nonstandard Abbreviations and Acronyms

DM   diabetes mellitus

with first acute MI, dyslipidemia is the second-most prevalent modifiable risk factor.[5] Thus, early identification of dyslipidemia and intervention to achieve optimal lipid levels early in life may be one of the most effective preventive and therapeutic strategies to reduce lifetime ASCVD risk. In this context, it is not surprising that the 2018 American College of Cardiology/American Heart Association guidelines on the management of blood cholesterol emphasize cholesterol screening in children and adolescents, with different recommended ages for screening based on cardiovascular risk factors, a family history of early cardiovascular disease, and low-density lipoprotein-cholesterol (LDL-C) level.[6] For adults aged 20 to 39 years, the guidelines recommend statin therapy for individuals with primary severe hypercholesterolemia (ie, LDL-C ≥190 mg/dL), since this patient population can accumulate massive long-term ASCVD burdens.[7]

However, relatively little evidence is available to stratify young adults at a high risk of ASCVD when their LDL-C levels are <190 mg/dL, although identifying predictive markers for ASCVD may be helpful to motivate healthy lifestyle habits in this population. Given that even moderate hypercholesterolemia can accelerate the development of atherosclerosis,[8] a subset of individuals with moderately but persistently elevated lipids might be at a higher risk of developing ASCVD. In fact, in the American College of Cardiology/American Heart Association cholesterol guidelines, persistently elevated LDL-C and/or triglyceride levels are included as risk-enhancing factors favoring the initiation of statin therapy in adults without diabetes mellitus (DM) aged 40 to 75 years with LDL-C levels of 70 to 189 mg/dL and 10-year ASCVD risks of 7.5% to 19.9% (intermediate risk) or 5.0% to 7.4% (borderline risk).[6] Persistently elevated LDL-C and triglyceride levels are defined as, optimally, 3 determinations of LDL-C ≥160 mg/dL and triglycerides ≥175 mg/dL, respectively, possibly because of their substantial variability.[6] This recommendation is supported by previous studies demonstrating an increased ASCVD risk in individuals with LDL-C ≥160 mg/dL and/or triglycerides ≥175 mg/dL.[9–12] However, in adults aged 20 to 39 years, the prognostic value of persistently elevated LDL-C and/or triglycerides has not been validated in a large, independent cohort, and thus, has not been incorporated into the current guidelines. Therefore, we hypothesized that persistently elevated levels of LDL-C and/or triglycerides might be associated with the risk of ASCVDs in statin-naive young adults aged 20 to 39 years without severe hypercholesterolemia. We tested this hypothesis in a nationwide population-based cohort study using the National Health Insurance Service (NHIS) database.

METHODS

The data are available from the Korean National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/) database which is open to researchers on request with approval by the Institutional Review Board.

Study Population

In this study, we used the NHIS database, which contains anonymized health-related information on ≈97% of Koreans.[13] Briefly, all Korean adults, except the 3% covered by the Medical Aid program, are encouraged to undergo standardized biennial health check-ups, providing data on demographics, lifestyle behaviors, and medical history; vital signs and anthropometric measurements; and laboratory analyses. The study population included Korean adults aged 20 to 39 years who had undergone ≥3 health examinations between January 1, 2009 and December 31, 2013.

Variables and Definitions

A questionnaire was used to obtain information on physical activities and cigarette and alcohol consumption. Regular physical activity was defined as any type of physical activity ≥5 times per week. Data on household income in percentiles were provided by the NHIS, and the bottom 20% was defined as having low household income. Obesity was defined as a body mass index ≥25 kg/m^2, according to the World Health Organization recommendations for Asians. DM was defined by the presence of elevated fasting glucose levels (≥126 mg/dL) or ≥1 claim per year for the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes for DM (E10-14) plus ≥1 claim per year for prescription of anti-diabetic medication. 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 *ICD-10* codes for hypertension (I10–I11), or ≥1 claim per year for prescription of antihypertensive medication. Stroke was defined by the use of its *ICD-10* codes (I63–I64) for diagnoses made during hospitalization plus claims for brain imaging tests, including magnetic resonance imaging and/or computerized tomography. MI was defined by the use of its *ICD-10* codes (I21-I22) during hospitalization or documentation of these diagnostic codes at least twice in outpatient records. Blood samples for the measurement of lipid profiles and glucose were drawn after an overnight fast. Lipid profiles, including the levels of total cholesterol, LDL-C, high-density lipoprotein-cholesterol (HDL-C), and triglycerides, were measured using an enzymatic method. Quality control of laboratory tests was conducted in accordance with the procedures of the Korean Association of Laboratory Quality Control.[14] Persistently elevated LDL-C and/or triglyceride levels were defined as ≥3 measures of LDL-C ≥160 mg/dL and/or triglycerides ≥175 mg/dL, respectively, as previously described.[6] For instance, individuals with 3 separate measures of LDL-C ≥160 mg/dL at 3 check-ups were considered as having persistently elevated LDL-C, while those with 2 measures of LDL-C ≥160 mg/dL and 1 measure of LDL-C <160 mg/dL at 3 check-ups were considered as not having persistently elevated LDL-C. After the final measurement of lipid levels during the baseline period (2009–2013), study participants were followed-up from baseline until the date of stroke or MI, or the end of the follow-up period (December 31, 2017), whichever came first. The primary outcome was a composite of incident fatal and non-fatal stroke and MI, and secondary outcomes were each component of the primary outcome.

Statistical Analysis

Descriptive statistics are presented as numbers (percentages) for categorical variables and means±SD or medians (with interquartile ranges) for continuous variables. For comparisons between groups, we used the χ^2 test or Fisher exact test for categorical variables, as appropriate, and 2-sample Student t-tests for continuous variables. Cox proportional hazards models were performed to assess associations between persistently elevated LDL-C and/or triglycerides and the risk of stroke and MI. Chronological trends in the risk of developing stroke and MI were expressed as Kaplan–Meier estimates and compared using the log-rank test according to the presence or absence of persistently elevated LDL-C or triglycerides. Hazard ratios (HRs) and 95% CIs were calculated in an unadjusted model, and then recalculated after adjusting for the pre-specified set of confounders. In model 1, we adjusted for age, sex, physical activity, smoking, alcohol consumption, income level, body mass index, hypertension, and DM. These 9 potential confounders were selected as covariates based on previous literature reporting factors associated with both exposure (lipid levels) and outcome (stroke and MI).[15–17] In model 2, we further adjusted model 1 for HDL-C levels. The interactions between variables were tested. In our main analyses, we censored participants who received statins during follow-up, to exclude the effects of statin therapy on lipid profiles. We also performed sensitivity analyses, where participants who received statin therapy during the follow-up period were not censored. Two-sided P values <0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of our institution (E-2001-040-1092). Written informed consent was waived because of its retrospective data

collection from an anonymized database, which allowed maintenance of the participants' confidentiality.

RESULTS

Population Characteristics

Among the 4 922 149 participants aged 20 to 39 years who underwent health examinations during 2012 to 2013, 1 991 977 individuals had undergone ≥3 health examinations during 2009 to 2013. To eliminate the confounding effects of statins on lipid levels, we excluded 32 705 individuals who were treated with statins during the baseline examination period. We also excluded 15 373 participants with missing values for lipid profiles and covariates. To mitigate potential reverse causality bias resulting from changes in lipid levels caused by pre-existing stroke or MI, 9575 participants with a history of stroke or MI during the baseline period (ie, 2009–2013) were excluded. We further excluded 46 471 participants with even 1 instance of LDL-C ≥190 mg/dL during 2009 to 2013, resulting in a final study population of 1 887 853 individuals (Figure 1). Individuals were censored if they received statins during follow-up (n=129 945). The mean age was 32.2 years, and 69.4% were men. Among the 1 887 853 participants with LDL-C levels <190 mg/dL, 11 121 (0.59%) and 167 373 (8.87%) had persistently elevated LDL-C (≥160 mg/dL) and triglyceride (≥175 mg/dL) levels, respectively. Compared with their counterparts, participants with persistently elevated LDL-C or triglyceride were older, more frequently men, had higher body mass index and waist circumference values, and were more likely to have hypertension and DM. Tables 1 and 2 summarize the characteristics of the study population according to the presence or absence of persistently elevated LDL-C or triglycerides.

Association of Persistently Elevated LDL-C and Triglyceride Levels With Study Outcomes

During a median follow-up of 5.2 years (interquartile range, 4.7–5.5), there were 2170 (0.23%) and 1537 (0.16%) incidences of stroke and MI, respectively. Unadjusted Kaplan–Meier plots are shown in Figure 2. The risk of the composite of stroke and MI was significantly higher in individuals with persistently elevated LDL-C ≥160 mg/dL than in those without (Figure 2A). Participants with persistently elevated LDL-C had a significantly higher stroke risk than those without, with the curves starting to diverge after ≈1 years of follow-up (Figure 2B). The risk of MI was significantly higher in individuals with persistently elevated LDL-C ≥160 mg/dL than in those without, with the curves starting to diverge after ≈3 years of follow-up (Figure 2C). The magnitude of the difference between the groups was greater for stroke than for MI (Figure 2B and 2C). Individuals with persistently elevated triglycerides ≥175 mg/dL
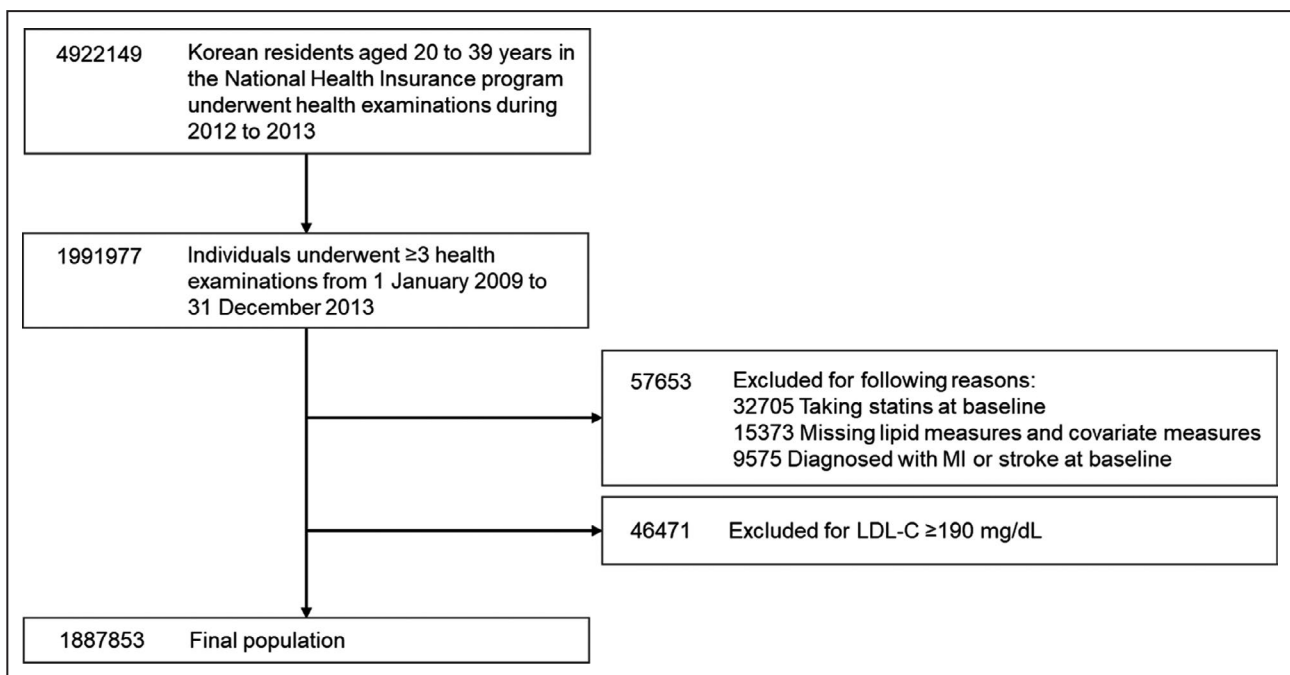

Figure 1. Flow diagram of the study population.
LDL-C indicates low-density lipoprotein cholesterol; and MI, myocardial infarction.

Table 1. Baseline Characteristics of Individuals According to Presence and Absence of Persistently Elevated LDL-C Levels

Characteristics	Persistently Elevated LDL-C ≥160 mg/dL		
	No (n=1 876 732)	Yes (n=11 121)	P Value
Age, y	32.2±4.3	34.4±3.4	<0.001
Male sex	1 299 751 (69.3)	10 048 (90.4)	<0.001
Urban residence	782 485 (41.7)	4545 (40.9)	0.078
BMI, kg/m²	23.4±3.6	25.8±3.5	<0.001
WC, cm	79.0±9.8	85.5±8.8	<0.001
Systolic BP, mm Hg	118.5±12.7	123.5±12.8	<0.001
Diastolic BP, mm Hg	74.6±9.1	78.2±9.3	<0.001
Hypertension	128 032 (6.8)	1440 (13.0)	<0.001
Diabetes mellitus	31 406 (1.7)	359 (3.2)	<0.001
Atrial fibrillation	372 (0.02)	2 (0.02)	0.891
CHF	1094 (0.06)	8 (0.07)	0.553
Regular PA*	328 630 (17.5)	2042 (18.4)	0.019
Smoking			<0.001
Never	921 531 (49.1)	3993 (35.9)	
Former	251 798 (13.42)	2109 (19.0)	
Current	703 403 (37.48)	5019 (45.1)	
Alcohol consumption			<0.001
0 g/d	610 382 (32.52)	3296 (29.6)	
1–30 g/d	1 098 923 (58.6)	6834 (61.5)	
>30 g/d	167 427 (8.92)	991 (8.9)	
Low-income level	178 688 (9.52)	900 (8.1)	<0.001
Hemoglobin, g/dL	14.6±1.5	15.3±1.2	<0.001
Glucose, mg/dL	91.3±14.5	95.4±19.3	<0.001
Mean TC, mg/dL	183.5±26.9	248.7±13.5	<0.001
Mean LDL-C, mg/dL	103.8±23.3	167.5±6.9	<0.001
Mean HDL-C, mg/dL	56.4±12.6	51.7±10.5	<0.001
Mean triglycerides†, mg/dL	100.3 (100.2–100.3)	137.5 (136.5–138.5)	<0.001
Creatinine, mg/dL	0.92±0.31	0.98±0.33	<0.001

Values given as number (percentage), mean±SD, or median (interquartile range) unless otherwise indicated. BMI indicates body mass index; BP, blood pressure; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; TC, total cholesterol; and WC, waist circumference.

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

†Geometric mean.

Table 2. Baseline Characteristics of Individuals According to Presence and Absence of Persistently Elevated Triglyceride Levels

Characteristics	Persistently Elevated Triglycerides ≥175 mg/dL		
	No (n=1 720 480)	Yes (n=167 373)	P Value
Age, y	32.0±4.4	34.4±3.4	<0.001
Male sex	1 147 774 (66.7)	162 025 (96.8)	<0.001
Urban residence	720 376 (41.9)	66 654 (39.8)	<0.001
BMI, kg/m²	23.1±3.5	26.4±3.3	<0.001
WC, cm	78.2±9.6	87.32±7.9	<0.001
Systolic BP, mm Hg	117.9±12.5	125.6±12.5	<0.001
Diastolic BP, mm Hg	74.1±9.0	79.6±9.2	<0.001
Hypertension	101 737 (5.9)	27 735 (16.6)	<0.001
Diabetes mellitus	22 783 (1.3)	8982 (5.4)	<0.001
Atrial fibrillation	324 (0.02)	50 (0.03)	0.002
CHF	969 (0.06)	133 (0.08)	<0.001
Regular PA*	302 807 (17.6)	27 865 (16.7)	<0.001
Smoking			<0.001
Never	890 255 (51.7)	35 269 (21.1)	
Former	224 923 (13.1)	28 984 (17.3)	
Current	605 302 (35.2)	103 120 (61.6)	
Alcohol consumption			<0.001
0 g/d	581 003 (33.8)	32 675 (19.5)	
1–30 g/d	999 130 (58.1)	106 627 (63.7)	
>30 g/d	140 347 (8.2)	28 071 (16.8)	
Low-income level	167 936 (9.8)	11 652 (7.0)	<0.001
Hemoglobin, g/dL	14.6±1.5	15.571.51	<0.001
Glucose, mg/dL	90.7±13.3	98.2±23.1	<0.001
Mean TC, mg/dL	181.6±81.61	207.5±27.6	<0.001
Mean LDL-C, mg/dL	103.7±23.4	109.0±26.5	<0.001
Mean HDL-C, mg/dL	57.4±7.001	45.9±5.0	<0.001
Mean triglycerides†, mg/dL	91.6 (91.6–91.7)	258.2 (257.8–258.5)	<0.001
Creatinine, mg/dL	0.9101.31	0.99±0.31	<0.001

Values given as number (percentage), mean±SD, or median (interquartile range) unless otherwise indicated. BMI indicates body mass index; BP, blood pressure; CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; TC, total cholesterol; and WC, waist circumference.

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

†Geometric mean.

had a significantly higher risk of the composite of stroke and MI than those without (Figure 2D). The risk of stroke was significantly higher in individuals with persistently elevated triglycerides than in those without, with the curves diverging <1 year of follow-up (Figure 2E). Individuals with persistently elevated triglycerides ≥175 mg/dL had a significantly higher MI risk than those without, with the curves starting to diverge after ≈1.5 years of follow-up (Figure 2F). The magnitudes of between-group differences for the

risk of MI were similar to those for stroke (Figure 2E and 2F).

Table 3 summarizes the adjusted risks of the composite of stroke and MI and each component in relation to persistently elevated LDL-C or triglycerides. In model 1, the risk of the composite of stroke and MI was significantly higher in participants with persistently elevated LDL-C than in those without (adjusted HR, 1.396; 95% CI, 1.005–1.940). The risk remained significantly higher after adjustment for HDL-C in model 2 (adjusted
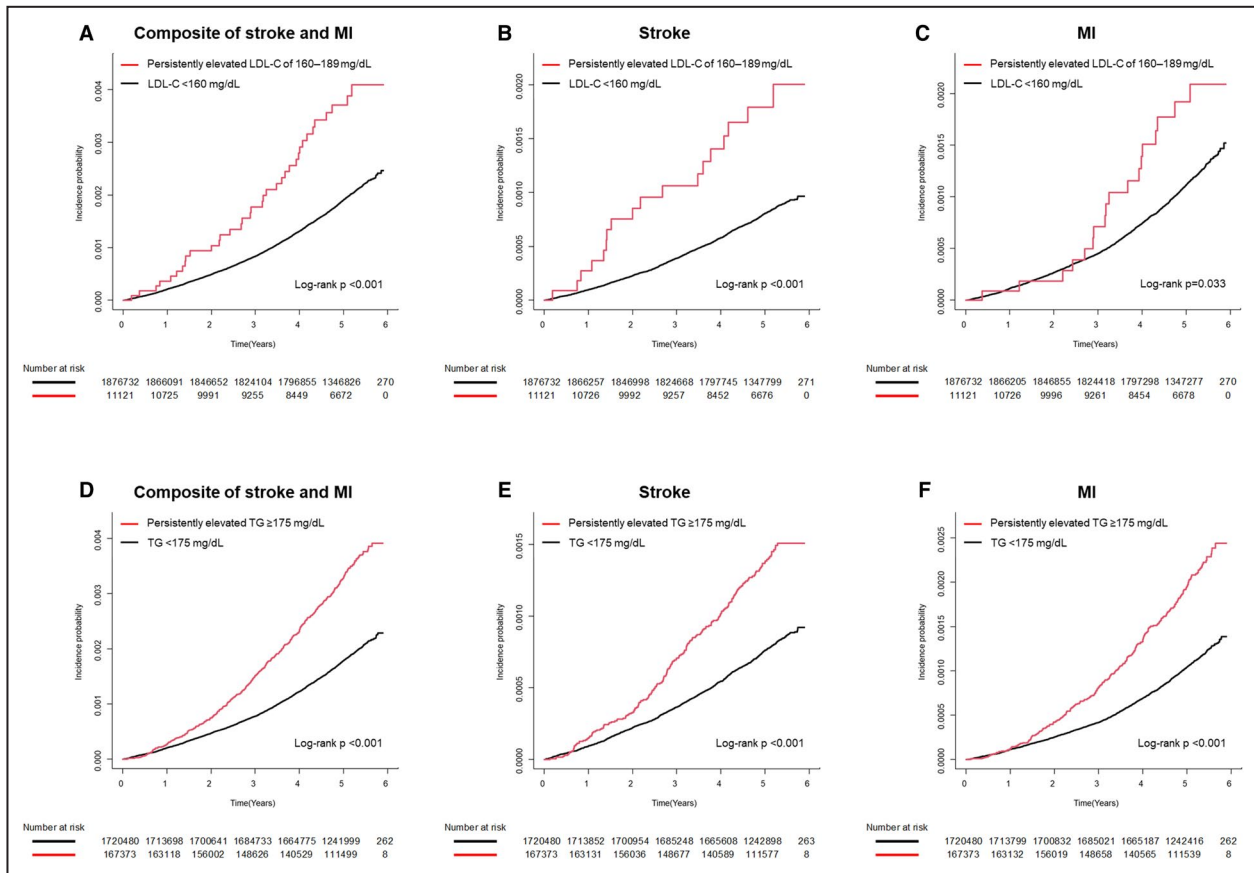
Figure 2. Kaplan–Meier plots for stroke and MI in the presence and absence of persistently elevated LDL-C or TG.
Unadjusted Kaplan–Meier curves for the composite of stroke and MI (**A** and **D**) and the individual outcome of stroke (**B** and **E**) and MI (**C** and **F**) based on the presence or absence of persistently elevated LDL-C (**A** through **C**) or TG (**D** through **F**). LDL-C indicates low-density lipoprotein cholesterol; MI, myocardial infarction; and TG, triglycerides.

HR, 1.395; 95% CI, 1.004–1.939). Participants with persistently elevated triglycerides had a significantly higher risk of the composite of stroke and MI than those without in model 1 (adjusted HR, 1.120; 95% CI, 1.015–1.236). However, after adjustment for HDL-C, the association between persistently elevated triglycerides and the composite outcome was attenuated (adjusted HR, 1.097; 95% CI, 0.992–1.212). With regard to each component of the primary outcome, stroke risk was significantly higher in participants with persistently elevated LDL-C than in those without in model 1 (adjusted HR, 1.627; 95% CI, 1.021–2.593) and model 2 (adjusted HR, 1.626; 95% CI, 1.021–2.592), while MI risk was not significantly different according to the presence or absence of persistently elevated LDL-C in both models. Individuals with persistently elevated triglycerides had a significantly higher risk of MI than those without in model 1 (adjusted HR, 1.152; 95% CI, 1.014–1.310), but statistical significance was attenuated after adjustment with HDL-C in model 2 (adjusted HR, 1.122; 95% CI, 0.986–1.277). The risk of stroke was not significantly higher in participants with persistently elevated

triglycerides than those without in either model 1 or model 2.

Joint Associations of Persistently Elevated LDL-C and Triglyceride Levels With Study Outcomes

To assess the independent and additive effects of persistently elevated LDL-C and triglycerides on study outcomes, the study participants were classified into 4 groups as follows: (1) LDL-C <160 mg/dL and triglyceride <175 mg/dL (n=1 711 369; 90.65%), (2) persistently elevated LDL-C only (n=9111; 0.48%), (3) persistently elevated triglycerides only (n=165 363; 8.76%), and (4) persistently elevated LDL-C and triglycerides (n=2010; 0.11%) (Table 4). The multivariable-adjusted risk of the composite of stroke and MI was significantly higher in persistently elevated LDL-C and triglycerides group than LDL-C <160 mg/dL and triglycerides <175 mg/dL group in both model 1 (adjusted HR, 1.930; 95% CI, 1.037–3.592) and model 2 (adjusted HR, 1.910; 95% CI,

Table 3. Adjusted HRs of Study Outcomes According to Presence and Absence of Persistently Elevated LDL-C and Triglyceride Levels

	Events	PY	IR	Model 1*		Model 2†	
				HR	95% CI	HR	95% CI
Composite of stroke and MI							
Persistently elevated LDL-C							
No	3645	9 420 521	0.387	1 (reference)	…	1 (reference)	…
Yes	36	49 455	0.728	1.396	1.005–1.940	1.395	1.004–1.939
Persistently elevated triglycerides							
No	3165	8 685 407	0.364	1 (reference)	…	1 (reference)	…
Yes	516	784 569	0.658	1.120	1.015–1.236	1.097	0.992–1.212
Stroke							
Persistently elevated LDL-C							
No	1519	9 423 339	0.161	1 (reference)	…	1 (reference)	…
Yes	18	49 466	0.364	1.627	1.021–2.593	1.626	1.021–2.592
Persistently elevated triglycerides							
No	1326	8 688 008	0.153	1 (reference)	…	1 (reference)	…
Yes	211	784 798	0.269	1.073	0.920–1.251	1.057	0.905–1.235
MI							
Persistently elevated LDL-C							
No	2152	9 421 982	0.228	1 (reference)	…	1 (reference)	…
Yes	18	49 477	0.364	1.204	0.756–1.916	1.203	0.756–1.915
Persistently elevated triglycerides							
No	1861	8 686 760	0.214	1 (reference)	…	1 (reference)	…
Yes	309	784 699	0.394	1.152	1.014–1.310	1.122	0.986–1.277

HR indicates hazard ratio; IR, incidence rate per 1000 person-years; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; and PY, person-year.
*Model 1 adjusted for age, sex, body mass index, smoking, alcohol consumption, physical activity, household income, diabetes mellitus, and hypertension.
†Model 2 adjusted as for model 1, plus high-density lipoprotein cholesterol.

1.026–3.555). Individuals in persistently elevated triglycerides only group had a significantly higher risk of the composite of stroke and MI than those in LDL-C <160 mg/dL and triglycerides <175 mg/dL group in model 1 (adjusted HR, 1.114; 95% CI, 1.009–1.231), but statistical significance was attenuated when adjusting for HDL-C in model 2 (adjusted HR, 1.091; 95% CI, 0.986–1.206). The risk of the composite of stroke and MI was higher in persistently elevated LDL-C only group than LDL-C <160 mg/dL and triglycerides <175 mg/dL group, although statistical significance was not achieved in both model 1 and 2.

Sensitivity Analyses

Our findings did not materially change in sensitivity analyses that did not censor participants who received statin therapy during the follow-up period (Figure 3 and Table 5). Briefly, the risk of the composite of stroke and MI was significantly higher in participants with persistently elevated LDL-C than in those without in model 1 (adjusted HR, 1.451; 95% CI, 1.097–1.919) and these results were unchanged

after adjustment for HDL-C in model 2 (adjusted HR, 1.451; 95% CI, 1.097–1.919). Participants with persistently elevated triglycerides had a significantly higher risk of the composite of stroke and MI than those without in model 1 (adjusted HR, 1.158; 95% CI, 1.060–1.266). The results were slightly attenuated but remained statistically significant in model 2 after adjustment for HDL-C (adjusted HR, 1.132; 95% CI, 1.034–1.239).

DISCUSSION

The main findings of this study, involving statin-naive adults aged 20 to 39 years, are as follows: (1) among participants with LDL-C <190 mg/dL, the proportion of individuals with persistently elevated LDL-C was small (0.59%) but the proportion of those with persistently elevated triglycerides was substantial (8.87%); (2) persistently elevated LDL-C levels of 160 to 189 mg/dL were independently associated with increased risks of the composite of stroke and MI and the individual outcome of stroke, regardless of adjustment for HDL-C; and

Table 4. Adjusted HRs of Study Outcomes in the 4 Groups Based on Status of Persistently Elevated LDL-C and/or Triglycerides

	Events	PY	IR	Model 1		Model 2	
				HR	95% CI	HR	95% CI
Composite of stroke and MI							
LDL-C <160 mg/dL and triglycerides <175 mg/dL	3139	8 644 300	0.363	1 (reference)	…	1 (reference)	…
Persistently elevated LDL-C only	26	41 107	0.633	1.298	0.882–1.911	1.294	0.879–1.905
Persistently elevated triglycerides only	506	776 221	0.652	1.114	1.009–1.231	1.091	0.986–1.206
Persistently elevated LDL-C and triglycerides	10	8348	1.198	1.930	1.037–3.592	1.910	1.026–3.555

Models adjusted for as in Table 3. HR indicates hazard ratio; IR, incidence rate per 1000 person-years; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and PY, person-years.

(3) persistently elevated triglyceride levels ≥175 mg/dL were independently associated with increased risk of composite of stroke and MI and the individual outcome of MI, but this association was attenuated after adjustment for HDL-C.

The accumulating adverse effects of high lipid levels on atheroma formation over a lifespan have been recognized for clinical importance,[18] and thus, early identification and treatment of high lipid levels can dramatically reduce the lifetime risk of ASCVDs.[19]
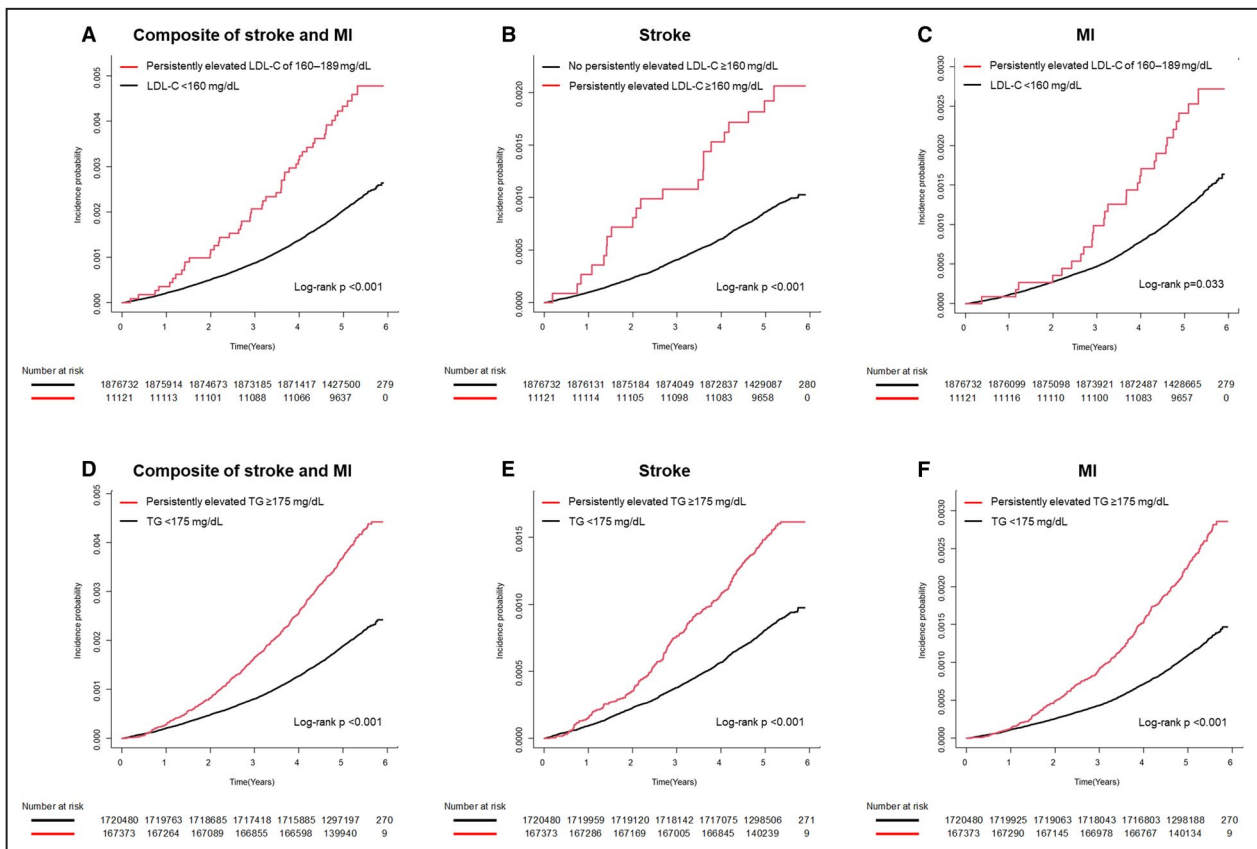

Figure 3. Kaplan–Meier plots for MI and stroke in the presence and absence of persistently elevated LDL-C or TG in sensitivity analyses not censoring participants receiving statins during follow-up periods.
Unadjusted Kaplan–Meier curves for the composite of stroke and MI (**A** and **D**) and the individual outcome of stroke (**B** and **E**) and MI (**C** and **F**) based on the presence or absence of persistently elevated LDL-C (**A** through **C**) or TG (**D** through **F**). LDL-C indicates low-density lipoprotein cholesterol; MI, myocardial infarction; and TG, triglycerides.

Table 5. Adjusted HRs of Study Outcomes According to Presence and Absence of Persistently Elevated LDL-C and Triglyceride Levels in Sensitivity Analyses Without Censoring Participants Who Received Statin Therapy During the Follow-up Period

	Events	PY	IR	Model 1		Model 2	
				HR	95% CI	HR	95% CI
Composite of stroke and MI							
Persistently elevated LDL-C							
No	4029	9 653 804	0.417	1 (reference)	…	1 (reference)	…
Yes	50	58 195	0.859	1.451	1.097–1.919	1.451	1.097–1.919
Persistently elevated triglycerides							
No	3419	8 842 468	0.387	1 (reference)	…	1 (reference)	…
Yes	660	869 531	0.759	1.158	1.060–1.266	1.132	1.034–1.239
Stroke							
Persistently elevated LDL-C							
No	1674	9 658 151	0.173	1 (reference)	…	1 (reference)	…
Yes	22	58 245	0.378	1.518	0.995–2.314	1.518	0.995–2.314
Persistently elevated triglycerides							
No	1441	8 846 119	0.163	1 (reference)	…	1 (reference)	…
Yes	255	870 277	0.293	1.052	0.913–1.212	1.034	0.895–1.193
Myocardial infarction							
Persistently elevated LDL-C							
No	2397	9 657 205	0.248	1 (reference)	…	1 (reference)	…
Yes	28	58 253	0.481	1.372	0.944–1.993	1.372	0.944–1.993
Persistently elevated triglycerides							
No	2011	8 845 394	0.227	1 (reference)	…	1 (reference)	…
Yes	414	870 064	0.476	1.238	1.105–1.386	1.204	1.073–1.350

HR indicates hazard ratio; IR, incidence rate per 1000 person-years; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; and PY, person-years.

Models adjusted for as in Table 3.

Indeed, young adults experiencing prolonged exposure to higher total cholesterol levels have a significantly higher lifetime risk of coronary heart disease, supporting the importance of lipid screening in this population.[20] One previous study demonstrated that the risk of cardiovascular events associated with elevated LDL-C was higher in younger individuals than in older individuals.[21] Furthermore, there is evidence of increasing stroke rates for individuals aged <50 years, despite a decreasing trend for stroke in the general population since 1950.[22] Importantly, in stroke survivors aged 18 to 49 years, long-term mortality (with up to 15 years of follow-up) was significantly higher than that in the general population, emphasizing the importance of preventing the development of stroke in young adults.[23] However, because of limited evidence, few recommendations exist on risk stratification and indications for primary preventative therapy in young adults, except for statin therapy for those with severe primary hypercholesterolemia, defined as LDL-C ≥190 mg/ dL. Specifically, according to the 2018 American College of Cardiology/American Heart Association

cholesterol guidelines, persistently elevated LDL-C ≥160 mg/dL is recognized as a risk enhancer in adults aged 40 to 75 years with LDL-C 70 to 189 mg/ dL and without DM at a 10-year ASCVD risk of 5% to 19.9%, but not in adults aged 20 to 39 years. Here, after excluding young adults with LDL-C ≥190 mg/ dL, we have demonstrated that the risk of the composite of stroke and MI and the individual outcome of stroke is independently and significantly increased in individuals with persistently elevated LDL-C levels ≥160 mg/dL. This suggests that young adults who have persistently elevated LDL-C levels ≥160 but <190 mg/dL, a generally accepted range for defining moderate hypercholesterolemia, have increased subsequent ASCVD risk. Although the proportion of individuals with persistently elevated LDL-C was small (11 121 [0.59%]), and subsequently, the absolute number of events in this group was small (18 strokes and 18 MIs), our study demonstrated that the increased risk of future ASCVD events was significant even with a relatively short follow-up period of 5.2 years. Notably, the 2019 European Society of Cardiology/European Atherosclerosis Society

dyslipidemia guidelines raised concerns about young adults not being treated adequately for dyslipidemia, since a low absolute risk might conceal a high relative risk to require at least intensive lifestyle changes,[24] supporting the importance of our findings. Furthermore, the difference in the risks of stroke and MI increased over time. It can thus be speculated that the lifetime risk of ASCVD among young adults with moderately but persistently elevated LDL-C may be substantially higher than the short-term risk estimates reported in our study, particularly when the condition is not appropriately managed. Future studies are needed to explore the possible benefits of statin use in this setting. Taken together, our study suggests that young adults with persistently elevated LDL-C levels ≥160 but <190 mg/dL should be considered candidates for aggressive intervention with statin therapy in combination with appropriate lifestyle modifications.

While elevated LDL-C is a well-established risk factor for ASCVD, the association between elevated triglycerides and ASCVD risk has been less clearly defined.[10] An important reason for this uncertainty is that there is no conclusive evidence whether elevated triglyceride levels directly cause ASCVD or are merely a surrogate for other metabolic abnormalities, such as obesity, insulin resistance, DM, and the accompanying lipoprotein abnormalities, particularly low HDL-C levels.[25] A meta-analysis reported that adjustment for established risk factors, especially HDL-C, substantially attenuated the magnitude of the association between high triglycerides and risk of coronary heart disease.[26] This is in line with our study, showing that the significant association between persistently elevated triglycerides and the composite of stroke and MI or the individual outcome of MI was attenuated after adjusting for HDL-C. In light of recent studies demonstrating a causative role for triglycerides in ASCVD development,[27,28] however, renewed attention has been paid to the clinical utility of triglyceride measurements. Indeed, the 2018 American College of Cardiology/American Heart Association cholesterol guidelines note that persistently elevated triglyceride levels are a risk enhancer in non-diabetic adults aged 40 to 75 years with LDL-C 70 to 189 mg/dL and with 10-year ASCVD risks of 5% to 19.9%.[6] Our study partly supports the extension of these recommendations to adults aged 20 to 39 years, by demonstrating that the effects of persistently elevated triglyceride levels ≥175 mg/dL and persistently elevated LDL-C levels ≥160 but <190 mg/dL were additive, in that participants with both findings were at the highest risk of the composite of stroke and MI. This result suggests that more attention should be paid on the screening and management of this lipid abnormality in young populations. Exploring the prognostic impacts of lifestyle changes or medications on the reduction of persistently elevated triglycerides will be a future topic of interest.

Strengths and Weaknesses of the Study

One of the strengths of the present study is that we showed the significant association of persistently elevated LDL-C and triglyceride levels with ASCVD risk in statin-naive young adults aged 20 to 39 years without severe hypercholesterolemia using a large nationwide population-based cohort study, in whom assessing this association is presumed challenging because of low event rates needed to achieve adequate statistical power. Our study also focused on evaluating the risk of ASCVD events according to persistently elevated LDL-C and triglyceride levels in statin-naive young adults, which are prevalent conditions found in this population but has been poorly investigated until now, whereas most previous studies have only examined the impact of single lipid values measured at baseline on prognosis. This difference is of clinical importance because the results of our study may contribute to further identify individuals at high risk for ASCVDs, particularly when individuals have mild or moderate abnormalities in their initial lipid levels and thus did not fulfill the indication for statin therapy by current guidelines.

Potential limitations warrant consideration. First, there are limitations inherent to the observational study design, such as selection bias, unmeasured confounders, and the inability to establish causality. Although we adjusted for a set of established cardiovascular risk factors, residual confounders could not be fully addressed. To alleviate concerns of reverse causality, however, individuals with previous stroke or MI were excluded. Second, since the study population was derived from a single country, the findings might not be generalizable to other ethnicities. Third, even with the large sample size of our study, the event rates of stroke and MI were still small, particularly in participants with both persistently elevated LDL-C and triglycerides, and thus, the absolute differences in event rates were not clinically meaningful. Since the effects of persistently elevated LDL-C and triglycerides appear to be cumulative, the real risk for stroke and MI might have been underestimated because of the relatively short follow-up period of our study, which is a limitation of the current NHIS database. Thus, considering that prolonged exposure to persistently elevated LDL-C or triglycerides in young adults may increase the risk of ASCVDs later in their life, the next step is to perform further studies with extended follow-up periods to determine the clinical importance of our findings. Fourth, the majority

of our study population was men (69.4%), and this sex imbalance was particularly pronounced among individuals with persistently elevated LDL-C (90.4%) or triglyceride levels (96.8%), which may limit the generalizability of our findings. Considering the sex difference in HDL-C,[29] further studies enrolling more women and performing sex-specific analysis are required. Fifth, we only reported the results of fatal and non-fatal MI and strokes as the relevant endpoints. Analyses for additional hard endpoints, such as all-cause and cardiovascular mortality, are needed in the future to draw more robust conclusions. Finally, this study is based on outcomes obtained from administrative data, which could be misleading. However, the accuracy of NHIS claims data for diagnosis of stroke and MI has been previously verified.[30,31]

Clinical and Public Health Implications

This study demonstrates that the efforts to achieve and maintain optimal LDL-C and triglyceride levels in young adults, even without severe hypercholesterolemia, could help to prevent future ASCVD events. Given that repeated measurements of lipid profiles are routinely used in clinical practice with the advantage of being simple and inexpensive to perform, persistently elevated LDL-C and triglyceride levels can be easily applied by clinicians in real-world settings to identify young adults at high risk of developing ASCVD and, in turn, to encourage adherence to healthy lifestyle habits.

CONCLUSIONS

In statin-naive young Korean adults aged 20 to 39 years, persistently elevated LDL-C ≥160 but <190 mg/dL was significantly associated with increased risks of the composite of stroke and MI and the individual outcome of stroke, regardless of HDL-C, although the proportion of individuals with this abnormal lipid profile was small. Persistently elevated triglycerides ≥175 mg/dL was relatively common in young adults with LDL-C levels <190 mg/dL, and this lipid abnormality was significantly associated with increased risks of the composite of stroke and MI and the individual outcome of MI, but this association was attenuated after adjustment for HDL-C.

ARTICLE INFORMATION

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