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Association of four lipid components with mortality, myocardial infarction, and stroke in statin-naïve young adults: A nationwide cohort study

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Abstract

Aims: Dyslipidaemia is a modifiable cardiovascular risk factor with prognostic implications. Current strategies for lipid management in young adults are largely based on expert recommendations. We investigated the risks of death and cardiovascular disease in relation to each lipid component to establish evidence for primary prevention in young adults.

Methods: In this nationwide population-based cohort study, we analysed 5,688,055 statin-naïve subjects, aged 20–39 years, undergoing general health check-ups between 2009 and 2014. The endpoint was a composite of clinical events including death, myocardial infarction (MI), and stroke. We compared the incidence and risk of clinical events according to each lipid variable.

Results: During follow-up (median 7.1 years), clinical events occurred in 30,330 subjects (0.53%): 16,262 deaths (0.29%), 8578 MIs (0.15%), and 5967 strokes (0.10%). The risk of clinical events gradually increased with increasing total cholesterol (TC) and triglycerides and decreasing high-density lipoprotein cholesterol (HDL-C), largely driven by MI. Low-density lipoprotein cholesterol (LDL-C) had a J-shaped association with clinical events, showing the lowest risk for LDL-C of 84–101 mg/dL. Among lipid variables, triglycerides remained the sole independent predictor (adjusted hazard ratio, 1.20; $p < 0.001$) after adjusting for conventional risk factors.

Conclusions: For statin-naïve young adults, the risk of clinical events was proportional to lipid levels, positively with TC and triglycerides, negatively with HDL-C, and J-shaped with LDL-C. Triglycerides had an independent and the strongest association with the clinical events. Screening and intervention for abnormal lipid levels, particularly triglycerides, from an early age might be of clinical value.

Keywords

Dyslipidaemia, nationwide population-based cohort, primary prevention, prognosis, young adult

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity worldwide, with high medical and socioeconomic burden.[1] Beyond the traditional treatment-centred approach, recent efforts have focused on disease prevention through early identification of the high-risk group and risk factor management. Dyslipidaemia is one of the major risk factors for CVD. Many studies have demonstrated that improvement of lipid profile leads to reduction in the risk of atherosclerotic CVD (ASCVD) and even mortality.[2–5] Because clinical ASCVD occurs mainly in middle-aged and older adults, previous guidelines have indicated which individuals of this age group could benefit from lipid management.[6,7] However, recent literature states that the cumulative exposure to lipids plays a central causative role in the initiation and progression of atherosclerosis; therefore, experts advise early screening and maintenance of the optimal lipid levels from young adulthood to achieve ideal cardiovascular health.[8–10] The latest guidelines for lipid management also emphasize estimation of lifetime cardiovascular risk, adherence to healthy lifestyles, and cholesterol screening early in life.[11,12] Nonetheless, objective verification of this issue among young adults aged 20–39 years is insufficient. The prevalence of dyslipidaemia in young adults varies across the region, but is rising faster than expected. Approximately 36% of adults aged 20 to 29 years and 43% of those aged 30 to 39 years in the US met the criteria for abnormal lipid levels as defined by *the National Cholesterol Education Program*.[13] Similarly, the *Korean Society of Lipid and Atherosclerosis* reported that a quarter of Korean adults in their 30 s had dyslipidaemia.[14] Therefore, solid evidence guiding clinical practice for lipid management is necessary in the young. We investigated the effect of lipid profiles on the risks of mortality, myocardial infarction (MI), and stroke in young adults aged 20–39 years to provide evidence for an appropriate lipid management strategy using a large population-based cohort.

Methods

Data source

We used the claims database from the National Health Insurance Service (NHIS) of South Korea. The NHIS is a mandatory national health insurance program administered by the Korean government, offering comprehensive medical care, including a standardized biennial health examination, to about 97% of the Korean population. The national health examination program consisted of self-reported surveys regarding health-related behaviours and medical histories, anthropometric measurements, and laboratory tests including the lipid profile. The quality control of the laboratory tests was conducted by *the Korean Association of Laboratory Quality Control* according to an act on health examinations. The medical care performed in Korea and the claims from NHIS are strictly assessed and are fed back by the Health Insurance Review and Assessment Service under the supervision of the Ministry of Health and Welfare. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of our institution (E-1901-112-1005). Informed consent was waived because anonymized health-related information from the NHIS claims database was retrospectively collected and assessed.[15]

Study population

From the NHIS database, we collected subjects aged 20–39 years who underwent the assigned health checkups between January 1, 2009 and December 31, 2014 ($n = 8{,}286{,}694$, 57.3% of all Koreans in this age group). Among them, 66,270 subjects using lipid-lowering medications at enrolment were excluded to avoid the confounding effects of medications on lipid variables and outcomes. In addition, 2,495,260 with missing values for at least one variable were excluded. Finally, to clarify the causal relationship between the lipid profile and clinical outcomes, 37,109 having a history of stroke or MI were excluded. Therefore, 5,688,055 individuals were included in the final analyses (Figure 1).

Study endpoint and follow-up

The study endpoint was a composite of clinical events, including newly detected all-cause death, MI, and stroke during follow-up. The study population was followed from the baseline health examination to the date of death, MI, stroke, or December 31, 2017, whichever came first. Death was defined as occurring from any cause, which was verified by death certificates and retrieved from the Statistics Korea database. MI was defined as diagnosis during hospitalization using ICD-10 codes (I21–I22) or these diagnostic codes appearing at least twice in outpatient medical records. Stroke was defined as diagnosis during hospitalization using ICD-10 codes (I63–I64) plus at least one claim for brain imaging studies including magnetic resonance imaging/angiography or computerized tomography. Subjects starting lipid-lowering medications during follow-up or those lost to follow-up were censored.

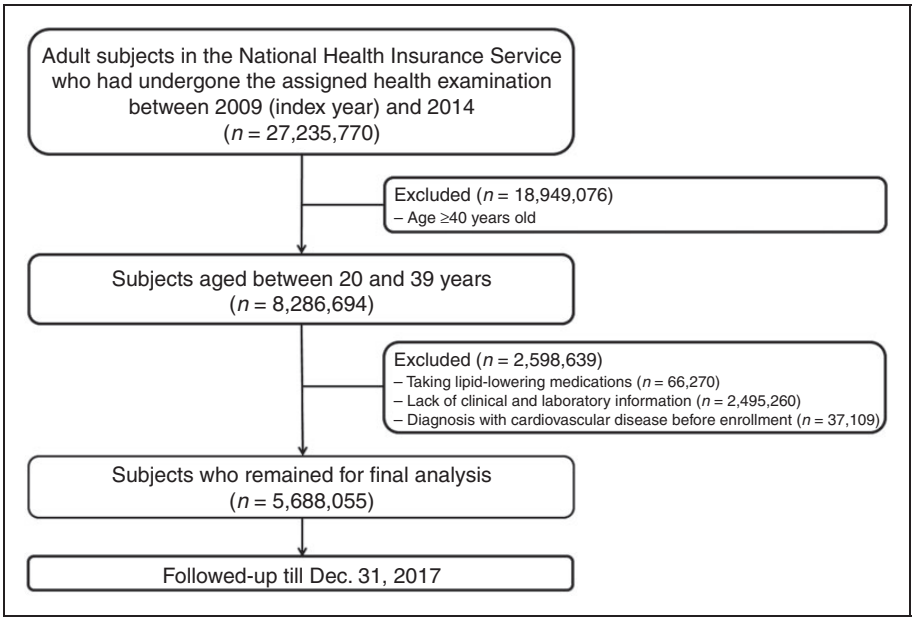

Figure 1. Schematic flow for study population enrolment.

Definitions of variables and Statistical analysis

Detailed methods are described in the Supplementary Text.

Results

Baseline characteristics

In the present cohort consisting of 5,688,055 statin-naïve individuals (mean age, 30.3 years; 60.8% male), 1,232,762 subjects (21.7%) had dyslipidaemia presenting with any of the following: total cholesterol (TC) $\geq$ 240 mg/dL, high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dL, low-density lipoprotein cholesterol (LDL-C) $\geq$ 160 mg/dL, and/or triglycerides $\geq$ 200 mg/dL. Subjects with dyslipidaemia were slightly older, more obese, less physically active, more likely to be men, had more experiences of smoking and alcohol, and had more family history of premature CVD versus their normolipidaemic counterparts. Hypertension and diabetes mellitus were observed in 12.3% and 3.9% of the dyslipidaemia group, respectively, with an approximately three-fold higher prevalence, while any malignancy at enrolment was less prevalent in the dyslipidaemia group (all $p < 0.001$). The mean/median (triglycerides) values of lipid profile were 206.1 (TC), 46.3 (HDL-C), 118.7 (LDL-C), and 182.0 (triglycerides) mg/dL in the dyslipidaemia group. Renal function assessed by serum creatinine and estimated glomerular filtration rate was worse in the dyslipidaemia than the normolipidaemia (Table 1).

Incidence and risk of clinical events

During a median follow-up of 7.1 years (interquartile range, 5.1–8.1 years), a composite of clinical events including all-cause death, MI, and stroke occurred in 30,330 subjects (0.53%): 16,262 deaths (0.29%), 8578 MIs (0.15%), and 5967 strokes (0.10%). The incidence of clinical events was significantly higher in the dyslipidaemia than in the normolipidaemia group (9488 (0.77%) vs 20,842 (0.47%); $p < 0.001$), the trend of which was consistent for all components of clinical events (4471 (0.6%) vs 11,791 (0.26%) for death; 3202 (0.26%) vs 5376 (0.12%) for MI; 1982 (0.16%) vs 3985 (0.09%) for stroke; all $p < 0.001$). Dyslipidaemia demonstrated a significant association with the increased risk of clinical events (crude hazard ratio (HR), 1.69; 95% confidence interval (CI), 1.65–1.73; $p < 0.001$).

When stratified by quartiles of each lipid variable (Table 2, Figure 2), TC, triglyceride, and HDL-C levels displayed a stepwise association with the incidence and risk of clinical events. Clinical events tended to occur more frequently in subjects with higher TC and triglycerides levels, and in those with lower HDL-C levels. The risks of clinical events increased by 47% and 108% in the highest quartiles (Q4) of TC and triglycerides, respectively, compared with each lowest quartile (Q1) as a reference. In contrast, HDL-C Q4 exhibited a 35% lower risk of clinical events than Q1. This tendency was more prominent for the risks of MI and stroke. Notably, triglycerides Q4 demonstrated $>$ two-fold higher risks for MI (crude

Table 1. Baseline characteristics of study population according to lipid profile at enrolment.

Variables	Total cohort ($n = 5,688,055$)	Dyslipidaemia ($n = 1,232,762$)	Normolipidaemia ($n = 4,455,293$)	p-value
Demographics				
Age, years	30.3 ± 5.1	32.1 ± 4.7	29.8 ± 5.1	<0.001
Man	3,458,182(60.8)	1,043,206 (84.6)	2,414,976 (54.2)	<0.001
Smoking				<0.001
Never	3,117,152 (54.8)	448,113 (36.4)	2,669,039 (59.9)	
Ex	581,067 (10.2)	160,201 (13.0)	420,866 (9.5)	
Current	1,989,836 (35.0)	624,448 (50.7)	1,365,388 (30.7)	
Alcohol drinking				<0.001
None	2,079,834 (36.6)	394,285 (32.0)	1,685,549 (37.8)	
Mild to moderate	3,171,825 (55.8)	701,743 (56.9)	2,470,082 (55.4)	
Heavy	436,396 (7.7)	136,734 (11.1)	299,662 (6.7)	
BMI, kg/m^2	23.0 ± 3.6	25.3 ± 3.6	22.9 ± 3.5	<0.001
BMI ≥ 25 kg/m^2	1,479,676 (26.0)	622,465 (50.5)	857,211 (19.2)	<0.001
WC, cm	77.5 ± 9.9	84.2 ± 9.2	75.6 ± 9.3	<0.001
Physical inactivity	3,086,755 (54.3)	683,057 (55.4)	2,403,698 (54.0)	<0.001
Urban residence	2,605,728 (45.8)	536,659 (43.5)	2,069,069 (46.4)	0.396
Income lower 20%	1,061,599 (18.7)	190,844 (15.5)	870,755 (19.5)	<0.001
Family history of premature CVD	374,294 (6.6)	95,236 (7.7)	279,058 (6.3)	<0.001
CAD	196,688 (3.5)	49,228 (4.0)	147,460 (3.3)	<0.001
CVA	202,607 (3.6)	52,688 (4.3)	149,919 (3.4)	<0.001
Systolic BP, mmHg	117.5 ± 13.0	122.6 ± 13.1	116.1 ± 12.6	<0.001
Diastolic BP, mmHg	73.6 ± 9.2	77.1 ± 9.5	72.7 ± 8.9	<0.001
Previous medical history				
Hypertension	352,610 (6.2)	151,020 (12.3)	201,590 (4.5)	<0.001
Diabetes mellitus	92,473 (1.6)	48,058 (3.9)	44,415 (1.0)	<0.001
Heart failure	2922 (0.05)	810 (0.07)	2112 (0.05)	<0.001
Atrial fibrillation	1165 (0.02)	311 (0.03)	854 (0.02)	0.803
Any malignancy	19,452 (0.3)	3733 (0.3)	15,719 (0.4)	0.013
Laboratory findings				
Hb	14.4 ± 1.6	15.1 ± 1.4	14.2 ± 1.6	<0.001
Total cholesterol	183.6 ± 33.0	206.1 ± 43.1	177.4 ± 26.4	<0.001
HDL-cholesterol	56.9 ± 13.8	46.3 ± 13.3	59.8 ± 12.4	<0.001
LDL-cholesterol	104.1 ± 29.4	118.7 ± 39.6	100.7 ± 25.5	<0.001
Triglyceride	114.0 (113.6–114.5)	182.0 (181.8–182.3)	79.8 (79.7–79.8)	<0.001
Fasting glucose	90.7 ± 15.1	94.9 ± 21.5	89.5 ± 14.1	<0.001
Creatinine	1.02 ± 0.9	1.06 ± 0.8	1.01 ± 0.9	<0.001
eGFR	97.4 ± 56.0	95.4 ± 57.2	97.9 ± 55.6	<0.001
Proteinuria	87,763 (1.5)	22,232 (1.8)	65,531 (1.5)	<0.001

Values are mean ± standard deviation, median (interquartile range) or n (%). Measurement units of laboratory findings are mg/dL, g/dL (for Hb), and ml/min/$1.73m^2$ (for eGFR).

BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular attack; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; Hb: haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; WC: waist circumference.

HR, 2.48) and stroke (crude HR, 2.53) and a 79% higher mortality risk (crude HR, 1.79) than Q1. Similarly, HDL-C Q4 reduced the risks of MI (crude HR, 0.49) and stroke (crude HR, 0.59) by approximately half, but the risk for death was only 22% lower (crude HR, 0.78) than Q1. Regarding LDL-C, a J-shaped association with clinical events was noted, with a slightly attenuated pattern by MI.

Table 2. The incidence and risk of clinical events according to lipid profile.

	Composite			Death			Myocardial infarction			Stroke		
	Event (n)	IR*	Crude HR (95% CI)	Event (n)	IR*	Crude HR (95% CI)	Event (n)	IR*	Crude HR (95% CI)	Event (n)	IR*	Crude HR (95% CI)
Total cholesterol												
Q1	6677	0.71	1.00 (ref)	3974	0.43	1.00 (ref)	1570	0.17	1.00 (ref)	1208	0.13	1.00 (ref)
Q2	6694	0.72	1.01 (0.97–1.04)	3781	0.42	0.96 (0.92–1.02)	1777	0.19	1.13 (1.06–1.21)	1261	0.14	0.96 (0.89–1.04)
Q3	7505	0.79	1.10 (1.07–1.14)	4037	0.43	1.00 (0.96–1.05)	2061	0.22	1.29 (1.20–1.37)	1521	0.16	1.17 (1.10–1.27)
Q4	9454	1.05	1.47 (1.42–1.51)	4470	0.50	1.17 (1.12–1.22)	3170	0.35	2.01 (1.97–2.22)	1977	0.22	1.63 (1.52–1.75)
P_{trend}			<0.001			<0.001			<0.001			<0.001
HDL-cholesterol												
Q1	9240	1.05	1.00 (ref)	4452	0.50	1.00 (ref)	3046	0.35	1.00 (ref)	1891	0.21	1.00 (ref)
Q2	8320	0.84	0.80 (0.78–0.83)	4493	0.45	0.90 (0.86–0.94)	2298	0.23	0.67 (0.64–0.71)	1662	0.17	0.79 (0.74–0.84)
Q3	6781	0.72	0.69 (0.67–0.71)	3832	0.41	0.81 (0.77–0.84)	1774	0.19	0.55 (0.52–0.58)	1303	0.14	0.65 (0.61–0.70)
Q4	5989	0.67	0.65 (0.63–0.67)	3485	0.39	0.78 (0.75–0.82)	1460	0.16	0.49 (0.46–0.52)	1111	0.12	0.59 (0.54–0.63)
P_{trend}			<0.001			<0.001			<0.001			<0.001
LDL-cholesterol												
Q1	7122	0.79	1.00 (ref)	4261	0.47	1.00 (ref)	1703	0.19	1.00 (ref)	1283	0.15	1.00 (ref)
Q2	6832	0.72	0.91 (0.88–0.94)	3793	0.40	0.83 (0.80–0.87)	1825	0.19	0.96 (0.92–1.03)	1297	0.14	0.92 (0.81–0.94)
Q3	7172	0.77	0.97 (0.91–1.00)	3869	0.42	0.86 (0.82–0.90)	1958	0.21	1.07 (1.00–1.14)	1461	0.16	1.04 (0.96–1.12)
Q4	9204	1.00	1.27 (1.24–1.31)	4339	0.47	0.93 (0.89–0.97)	3092	0.34	1.47 (1.38–1.56)	1926	0.21	1.27 (1.19–1.37)
P_{trend}			<0.001			0.006			<0.001			<0.001
Triglycerides												
Q1	5209	0.56	1.00 (ref)	2987	0.32	1.00 (ref)	1380	0.15	1.00 (ref)	898	0.10	1.00 (ref)
Q2	6316	0.69	1.22 (1.18–1.26)	3612	0.39	1.22 (1.16–1.28)	1605	0.18	1.20 (1.08–1.25)	1199	0.13	1.34 (1.23–1.46)
Q3	8002	0.85	1.50 (1.45–1.55)	4366	0.46	1.40 (1.37–1.50)	2156	0.23	1.51 (1.41–1.62)	1599	0.17	1.73 (1.59–1.87)
Q4	10,803	1.18	2.08 (2.02–2.15)	5297	0.58	1.79 (1.71–1.87)	3437	0.38	2.48 (2.33–2.64)	2271	0.25	2.53 (2.34–2.73)
P_{trend}			<0.001			<0.001			<0.001			<0.001

*Incidence rate was calculated as 1000 person-years.

CI: confidence interval; HDL: high-density lipoprotein; HR: hazard ratio; IR: incidence rate; LDL: low-density lipoprotein; Q: quartile; ref: reference.

The second lowest quartile (Q2) of LDL-C (84–101 mg/dL) had the lowest risk of the composite of clinical events (crude HR, 0.91) and of each component of those clinical events (death crude HR, 0.83; MI crude HR, 0.96; stroke crude HR, 0.92). LDL-C Q4 demonstrated increased risks for MI and stroke by 47% and 27%, respectively.

Kaplan–Meier curves for incidence probability also demonstrated that subjects in Q4 of TC, triglycerides, and LDL-C and those in Q1 of HDL-C had the worst prognosis, regardless of the type of clinical event (all log-rank $p < 0.001$) (Figure 3).

Triglycerides as a powerful predictor in young adults

Other than dyslipidaemia, age, male sex, unhealthy lifestyle behaviours (current smoking, heavy drinking, and obesity), family history of CVD, and history of hypertension, diabetes mellitus, and chronic serious diseases were significantly associated with the occurrence of the composite of clinical events in young adults (Table 3). The highest quartiles of TC, triglycerides, and LDL-C also revealed a significant association with clinical events, largely driven by MI. In particular, triglycerides had the strongest predictive value for clinical events. However, HDL-C Q4 showed a protective effect. After adjusting for age and sex (model 1), TC Q4 (adjusted HR, 1.11; $p < 0.001$) and triglycerides Q4 (adjusted HR, 1.25; $p < 0.001$) were independently associated with the risk of clinical events, but LDL-C Q4 and HDL-C Q4 were not. Furthermore, after adjusting for age, sex, smoking, heavy drinking, obesity, physical inactivity, family history of premature CVD, and history of hypertension and diabetes mellitus, all of which were conventional cardiovascular risk factors with significant associations in the univariable analysis (model 2), triglycerides remained the sole independent determinant of clinical events (adjusted HR, 1.20; $p < 0.001$). Similar patterns were observed regarding mortality, MI, and stroke (Supplementary Table 1).

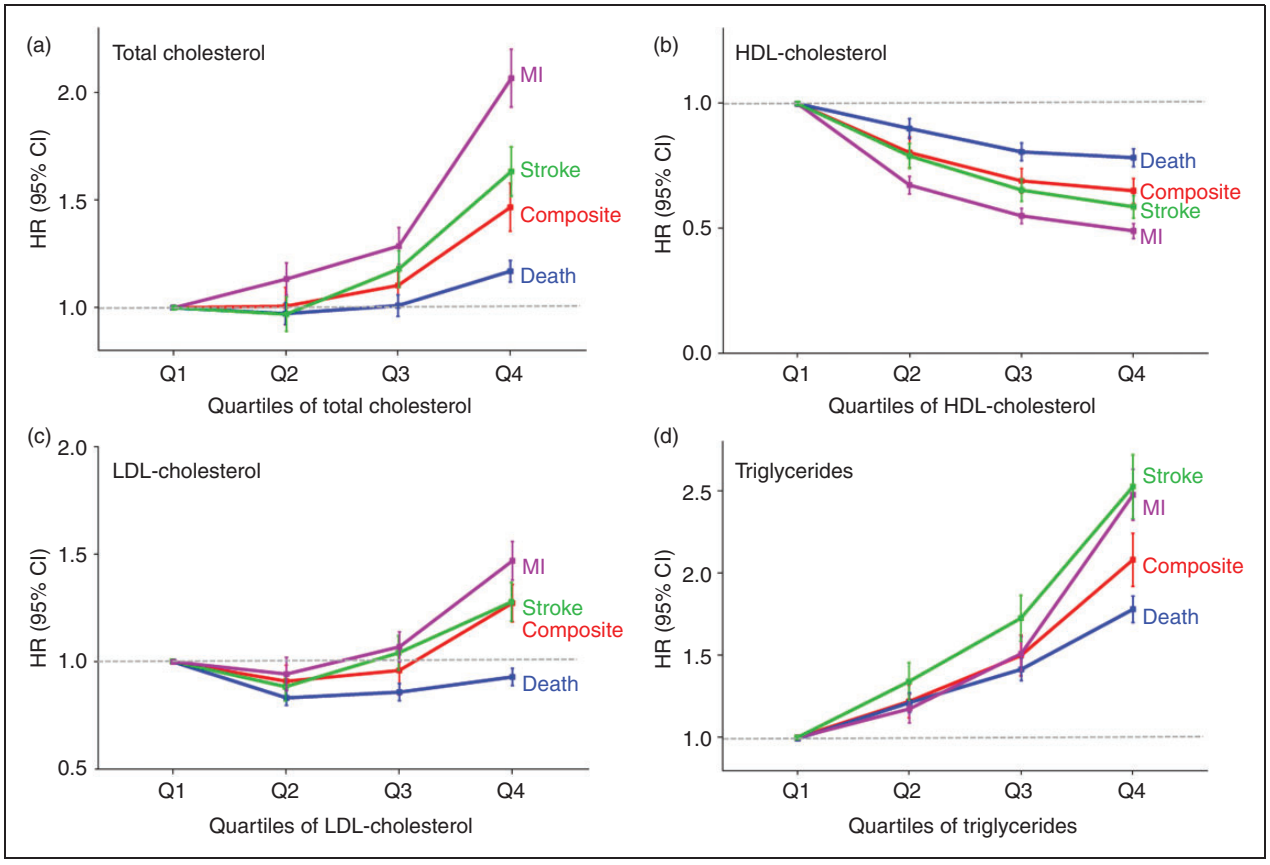

Figure 2. The risk of clinical events, including death, MI, and stroke according to quartiles of lipid variables. The risk of clinical events according to quartiles of each lipid variable is illustrated in a dose-dependent manner by TC (a), HDL-C (b), and triglycerides (d) levels, while in a J-shaped pattern by LDL-C (c). The red solid line represents the composite of clinical events, the blue solid line is death, the purple solid line is MI, and the green is stroke.
MI: myocardial infarction; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Q: quartile; HR: hazard ratio; CI: confidence interval.

Furthermore, when more strict definition of stroke (diagnostic codes (I63–I64) plus ≥ 2 claim for brain imaging studies) was adopted, the risks of stroke in relation to lipid variables were not different from those under the original definition (Supplementary Table 2). The sex-specific analysis generally showed results similar to those of the total cohort (Supplementary Table 3). Of note, it is worth mentioning that triglycerides were more highly associated with the risk of stroke in women, whereas TC and triglycerides were more highly associated with the risk of MI in men. Therefore, it is conceivable that the effects of dyslipidaemia can be variable according to sex. When stratified by deciles of triglycerides, the most powerful lipid variable from this cohort, the incidence rate of clinical events gradually increased, with statistical significance achieved only in the 10th percentile group (Supplementary Figure). Evidently, the risk of stroke showed a consistent increase with all HR > 1.0, whereas that of MI had a steep increase in the 10th percentile group, suggesting differential effects of triglycerides on CVD (i.e. threshold effects on cardiac events versus stepwise effects on cerebrovascular events).

Discussion

The main findings of the present study are as follows: during a median follow-up of 7.1 years, 1) higher TC and triglycerides, and lower HDL-C, were significantly associated with the clinical events (death, MI, and stroke); 2) a J-shaped association between LDL-C and the clinical events was noted, with the lowest risk for LDL-C of 84–101 mg/dL; and 3) among the lipid variables, triglycerides was an independent and the strongest predictor of clinical events after adjusting for conventional risk factors. This is the largest-ever cohort study in statin-naïve young adults demonstrating the close link between the risks of death, MI, and stroke and the lipids. Also, this study presents a novel meaning of lipid variables, particularly triglycerides and LDL-C. Our findings suggest triglycerides as a main screening and potential therapeutic target, highlight the role of dyslipidaemia on

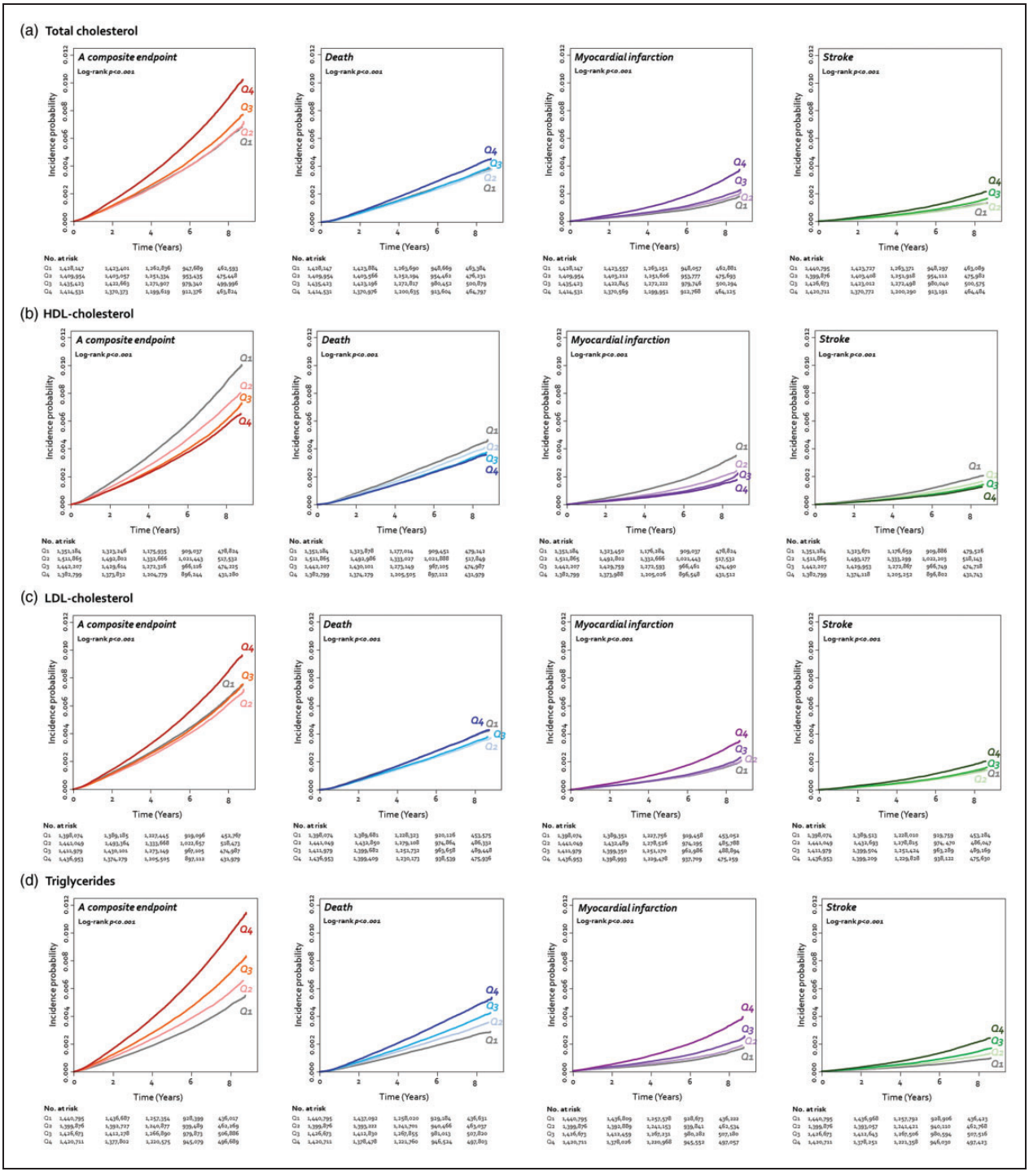

Figure 3. Kaplan–Meier curves for the incidence probability of clinical events according to quartiles of lipid variables. The incidence probability of the composite of clinical events tended to increase with higher TC and triglycerides, and lower HDL-C. In terms of LDL-C, the second-lowest quartile (pale orange solid line in (c)) showed the lowest incidence probability. Commonly, the highest quartile of TC (a), LDL-C (c), and triglycerides (d), and the lowest quartile of HDL-C (b) had the worst prognosis.
MI: myocardial infarction; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Q: quartile.

Table 3. Cox analysis for the risk of clinical events.

Univariable analysis		
Variables	Unadjusted HR (95% CI)	*p*-value
Age (per five-year increment)	1.39 (1.37–1.41)	<0.001
Male sex	1.96 (1.91–2.02)	<0.001
Current smoking	1.98 (1.94–2.03)	<0.001
Severe drinking	1.63 (1.57–1.68)	<0.001
BMI $\geq$25 kg/m^2	1.55 (1.51–1.58)	<0.001
Physical inactivity	0.99 (0.97–1.02)	0.562
Income lower 20%	1.10 (1.07–1.13)	<0.001
Family history of CVD	1.35 (1.29–1.40)	<0.001
Hypertension	2.45 (2.37–2.53)	<0.001
Diabetes mellitus	2.86 (2.70–3.02)	<0.001
Atrial fibrillation	4.95 (3.46–7.07)	<0.001
ESRD	5.66 (3.61–8.87)	<0.001
Any malignancy	4.08 (3.70–4.51)	<0.001
Dyslipidaemia	1.69 (1.65–1.73)	<0.001
Total cholesterol Q4	1.42 (1.38–1.45)	<0.001
HDL-cholesterol Q4	0.78 (0.76–0.81)	<0.001
LDL-cholesterol Q4	1.32 (1.29–1.35)	<0.001
Triglycerides Q4	1.67 (1.64–1.71)	<0.001
Multivariable analysis		
Models	Adjusted HR (95% CI) of cholesterol	*p*-value
*Model 1**		
Total cholesterol Q4	1.11 (1.07–1.15)	<0.001
HDL-cholesterol Q4	0.96 (0.90–1.03)	0.309
LDL-cholesterol Q4	1.02 (0.99–1.06)	0.267
Triglycerides Q4	1.25 (1.21–1.28)	<0.001
Model 2†		
Total cholesterol Q4	1.06 (0.99–1.10)	0.101
HDL-cholesterol Q4	1.01 (0.95–1.09)	0.646
LDL-cholesterol Q4	1.06 (0.98–1.14)	0.171
Triglycerides Q4	1.20 (1.14–1.26)	<0.001

Multivariable models were adjusted for age and sex*, age, sex, current smoking, heavy drinking, physical inactivity, family history of premature CVD, hypertension, and diabetes mellitus†, respectively.
BMI: body mass index; CI: confidence interval; CVD: cardiovascular disease; ESRD: end-stage renal disease; HDL: high-density lipoprotein; HR: hazard ratio; LDL: low-density lipoprotein; Q: quartile.

short-term prognosis, and help establish an appropriate lipid management strategy as primary prevention for adults aged 20–39 years.

Impact of dyslipidaemia on clinical events in young adults

Differences in the cardiovascular risk burden from an early age can amplify the differences in the lifetime risk of CVD, especially after middle-age.[16] Previous studies have demonstrated that dyslipidaemia in young adulthood could increase the risk of ASCVD later in life.[17–19] Klag et al. reported a strong association between TC levels measured in 1017 young men and subsequent CVD during midlife in a prospective study with a median follow-up of 30.5 years.[17] More recently, combined data from three cohorts of men younger than 40 years showed a graded relationship between TC levels and long-term risk of death from coronary, cerebrovascular, and any cause.[18] All of these studies

consistently highlighted the cumulative effects of abnormal lipid levels since young adulthood as a determinant of ASCVD after midlife, supporting the necessity of early screening of blood lipid levels. Therefore, recent lipid guidelines recommend that timely screening for children and adolescents could be reasonably considered, although a subject is presumed to be at low-risk in the absence of cardiovascular risk factors or family history of premature CVD.[7,11,12] However, evidence-based specific recommendations for lipid management in young adults aged 20–39 years are scarce.[7,11,12]

This study demonstrated that dyslipidaemia was significantly associated with an increased risk of clinical events in 'statin-naïve' young adults. In this cohort, 21.7% of young adults had dyslipidaemia, similar to that reported by the *Korean Society of Lipid and Atherosclerosis*.[14] Among the young adults with dyslipidaemia but without exposure to statins ($n = 1{,}232{,}762$), the incidence rate of the study endpoint was 4.86 per 1000 person-year: 2.28 for death, 1.65 for MI, and 1.02 for stroke. Although the overall incidence of clinical events for young adults is not as high as that for middle-aged or older adults, medical and socioeconomic burdens cannot be overlooked because young adults comprise the base of the economic population in a society, and the prevalence of CVD is increasing in this age group.[20,21]

Of note, the present study revealed that the majority of clinical events occurred before the age of 45 years. Thus, unlike the earlier reports showing the effect of dyslipidaemia detected in their 20 s on midlife CVD,[17–19] the present study suggests that dyslipidaemia could determine clinical events earlier in life. Therefore, dyslipidaemia could be involved in short-term as well as long-term prognosis for young adults, and earlier and active intervention for lipids might be beneficial to improve the prognosis. Another remarkable finding involved the differential effect of dyslipidaemia on each component of the clinical events. Understandably, dyslipidaemia was more influential on the risks of MI and stroke, thereby justifying its role in promoting the initiation and progression of atherosclerosis.[22] In addition, attention needs to be paid to the differential effects of dyslipidaemia according to sex – that is, triglycerides were more highly associated with the risk of stroke in women, whereas TC and triglycerides had a stronger effect on the risk of MI in men. Regarding premature death, the effects of dyslipidaemia on mortality seem to be relatively mitigated because the two most common causes of death for individuals in their 20 s and 30 s in South Korea are traffic accidents and suicide.[23] This observation can also be supported by previous studies showing comparatively favourable prognoses for patients experiencing ASCVD related to dyslipidaemia at a young age.[24,25]

Triglycerides as a new screening and potential therapeutic target in young adults

In the present study, triglycerides and HDL-C were consistently associated with the risks of MI, stroke, and mortality in a dose-dependent manner, even within normal range (Table 2, Figure 2). Data from previous studies involving young populations showed that triglycerides and HDL-C have a close relationship with CVD, consistent with our findings.[26–28] The CARDIA study reported that premature exposure to non-optimal triglycerides ($\geq$150 mg/dL), corresponding to the highest quartile of our study, showed a strong association with coronary artery calcification as a surrogate marker for coronary heart disease (CHD).[26] In a study involving Danish men with first acute MI before age 45 years, approximately half had abnormal lipid profiles matching high triglycerides and low HDL-C.[27] Kivioja et al. also proved that high triglycerides and low HDL-C were risk factors for early onset stroke in 961 patients 25–49 years of age.[28] From a practical viewpoint, it is noteworthy that the predictive value of triglycerides was the most powerful lipid component for CVD in our cohort, and, further, was not attenuated after adjusting for conventional cardiovascular risk factors. This was also confirmed in subjects without serious chronic illnesses, implicating triglycerides as a key player of premature death. Since, until now, hypertriglyceridaemia has been regarded as a by-product of common metabolic disorders, including elevated TC and LDL-C, and unhealthy lifestyle behaviours such as heavy drinking, obesity, and physical inactivity, the direct correlation between triglycerides and cardiovascular events has been controversial and has had low clinical priority.[29] The current study is believed to suggest the causal role of triglycerides in developing ASCVD, given the observation of the recent Mendelian randomization studies.[30–32] In addition, the strong prognostic value of triglycerides demonstrated in our study supports the renewed interest in triglycerides as the main screening and potential therapeutic target for the young adults.[33,34] This emphasizes the importance of healthy lifestyle behaviours to lower triglyceride levels during young adulthood.

Unexpectedly, LDL-C increased the risk of clinical events in a J-shaped pattern. Furthermore, the LDL-C Q2 (84–101 mg/dL) ensured the greatest total risk reduction but was not statistically convincing regarding an MI risk. This stood aside from the general principle of LDL-C, 'the lower, the better',[10,12] proposing that the optimal LDL-C level for young adults might be reconsidered. Possible explanations include the independent role of the lipoprotein(a), which has not been measured in this study,[35] and the increased risk of death from other cardiovascular causes such as

cancer, at an LDL-C < 84 mg/dL.[36,37] Although a recent study presented a stepwise increase in CHD according to the baseline LDL-C in young adults,[19] this did not refute our results because its reference value was defined as LDL-C < 100 mg/dL, without further categorization. Moreover, the top quartile of LDL-C in our study showed a clear increase in the risk of CVD, which was in agreement with previous studies, where higher LDL-C was significantly associated with an increased risk of ASCVD.[19,28,38] Thus, this might add evidence supporting expanding statin prescriptions to young adults in conjunction with intensive lifestyle modifications. Further studies are required to explore the beneficial effects of statins in this age group.

Study limitations

First, there are limitations related to the observational retrospective design using the claims database. However, definitions by the diagnostic codes from the NHIS database were previously validated, and similarly used in numerous prior studies.[15,39,40] In addition, subject selection did not seem skewed because the clinical characteristics and prevalence of dyslipidaemia were not different from those of the complete enumeration by the *Korean Society of Lipid and Atherosclerosis*.[14] To clarify the causality, subjects taking statins before enrolment and those who had experienced MI or stroke were excluded, and those starting statins during follow-up were also censored. Second, as study participants were exclusively from Korea, international studies including multiple ethnic groups will be needed to validate and generalize our results. Lastly, detailed information on the cause of death was not provided due to the innate limitation of our cohort, and, thus, we could not analyse the competing risk of death. The differences in the effect of lipids according to the specific cause of death are worthy of being investigated in the future.

Conclusions

In the largest-ever cohort involving 'statin-naïve' young adults aged 20–39 years, the risks of death, MI, and stroke were significantly associated with each lipid component. In particular, triglycerides emerged as an important screening and a potential therapeutic target in the primary prevention setting of this age group. These adduce evidence that earlier screening and active intervention could assist in achieving ideal cardiovascular health, preventing subsequent ASCVD, and providing a better prognosis in this population.

Author contribution

Conception and design was carried out by HL, JBP, KH, and HKK; data acquisition was carried out by HL, JBP, KH, and HKK; data analysis and interpretation was performed by HL, JBP, KH, and HKK; statistical analysis was carried out by HL, KH, and HKK; HL and HKK drafted and finalized the paper; critical revision of the paper for important intellectual content was carried out by ICH, YEY, HEP, SYC, YJK, and GYC.

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