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Effect of total cholesterol level variabilities on cerebrovascular disease

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Abstract. – OBJECTIVE: Hyperlipidemia is a risk factor of cerebrovascular disease (CVD). However, the relationship between CVD and cholesterol variability is less clear. This study assesses the relationship between cholesterol change and CVD risk.

PATIENTS AND METHODS: We reviewed 480,830 people from 20 to 99 years with 2 health check-ups from 2002 to 2015 from the Korean National Health Insurance (KNHI) database. People's baseline and follow-up cholesterol levels were classified into low (<180 mg/dL), moderate (≥180 mg/dL and <240 mg/dL), and high (≥240 mg/dL). Participants were divided into 9 groups (low-to-low, low-to-moderate, low-to-high, moderate-to-low, moderate-to-moderate, moderate-to-high, high-to-low, high-to-moderate, high-to-high).

RESULTS: Low to high cholesterol level is associated with hemorrhagic stroke (aHR1 = 1.59; 95% CI 1.12-2.28 and aHR2 = 1.56; 95% CI 1.07-2.25). Low to moderate/high cholesterol level is associated with ischemic stroke and occlusion/stenosis (for low to moderate, aHR1 = 1.11; 95% CI 1.04-1.17 and aHR2 = 1.14; 95% CI 1.07-1.21 for ischemic stroke and aHR1 = 1.18; 95% CI 1.07-1.29 and aHR2 = 1.20; 95% CI 1.08-1.32 for occlusion/stenosis, for low to high, aHR1 = 1.42; 95% CI 1.20-1.67 and aHR2 = 1.28; 95% CI 1.08-1.52 for ischemic stroke and aHR1 = 1.86; 95% CI 1.46-2.36 and aHR2= 1.74; 95% CI 1.36-2.23 for occlusion/stenosis). Moderate to high cholesterol level is associated with ischemic stroke and occlusion/stenosis (for ischemic stroke, aHR1 = 1.12; 95% CI 1.05-1.20 and aHR2 = 1.10; 95% CI 1.03-1.17, for occlusion/stenosis, aHR1 = 1.21; 95% CI 1.10-1.33 and aHR2 = 1.19; 95% CI 1.08-1.32). Moderate to low cholesterol level is associated with ischemic and hemorrhagic stroke and occlusion/stenosis (for ischemic, aHR1 = 1.15; 95% CI 1.09-1.21, for hemorrhagic, aHR1 = 1.14; 95% CI 1.01-1.28, for occlusion/stenosis, aHR1 = 1.14; 95% CI 1.05-1.23). High to low cholesterol level is associated with ischemic stroke and occlusion/stenosis (for ischemic stroke, aHR1 = 1.51; 95% CI 1.33-1.71 and aHR2 = 1.20; 95% CI 1.05-1.36, for occlusion/stenosis, aHR1 = 1.50; 95% CI 1.24-1.81).

CONCLUSIONS: Our study shows that cholesterol changes, especially larger changes, lead to an increase in CVD, which demonstrates that cholesterol variability may increase CVD.

Key Words:
Cholesterol, Cerebrovascular disease, Hyperlipidemia.

Introduction

Stroke refers to a permanent ischemic or hemorrhagic injury of a cerebral vascular territory based on radiological, pathological, and/or clinical evidence[1]. Stroke is the second most common cause of mortality which accounts for up to 11.1% of death and caused about 5.8 million death in 2010 worldwide, roughly splitting equally between ischemic and hemorrhagic stroke[2]. Also, stroke is the third most common cause of disease burden as calculated by disability-adjusted life years, with hemorrhagic stroke-causing 2.5% and ischemic stroke causing 1.6% of total disease burden worldwide[3].

While there is evidence that strokes among the elderly have been declining over periods globally[4,5], there have been possible findings where strokes among young adults are increasing[5-7]. Since up to 85% of all strokes could be preventable with modifications of risk factors including hypertension, smoking, diabetes, alcohol intake, diet, and physical activities[8], modifications of risk factors

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for stroke prevention must be executed properly. One of those risk factors to be monitored is dyslipidemia. There have been many epidemiological studies[9,10] suggesting dyslipidemia to be one of the main stroke risk factors. Furthermore, studies[11-13] have found that cholesterol-lowering agents, particularly statins, reduce strokes where the use of statin can lead to up to a 31% reduction of strokes and statin has been used as one of the preventive medications for ischemic stroke. However, scholars[14] on the relationship between dyslipidemia and stroke have been mostly conducted on middle-aged/elderly populations and there has been insufficient evidence on the advantages/disadvantages of finding and treating dyslipidemia in younger individuals.

Some studies[15-17] showed dyslipidemia is present in 12%-13% of young adults and that hyperlipidemia confers a higher risk of stroke in the younger population. In addition, there was a correlation between the decrease in total cholesterol and a decreased risk of cardiovascular disease[18,19]. This suggests a possible similar association between total cholesterol and stroke because cardiovascular disease, like stroke, is associated with dyslipidemia. Especially, an increase in total cholesterol level to 240 or above is correlated with a 21% increase in ischemic heart disease[20,21]. While those findings suggest a need to modify dyslipidemia among young adults as well, there have not been enough studies with diverse age groups to elucidate the relationship between cholesterol change and stroke risk.

Thus, this paper seeks to determine the correlation between cholesterol change and stroke risk using a nationwide database covering multi-million populations with a wide range of ages.

Patients and Methods

Study Population

Database source

This retrospective nationwide population-based study was performed using the Korean National Health Insurance (KNHI) database, which covers approximately 50 million Korean people. The KNHI database includes medical information of each participant including demographics, clinical diagnoses (per ICD-10), prescribed medications, blood pressure, lipid profile, fasting glucose, height, weight, body-mass index (BMI), physical activity, smoking history, alcohol consumption, income, and family history.

We reviewed the KNHI database for all people who were >20 years old from 2002. We identified 480,830 participants who had two health check-ups, the first one on the period from 2002 to 2008 and the second one from 2009 to 2015. We excluded people with no cholesterol level data (n=629), the deceased population (n=14,980), and people with cerebrovascular disease (CVD) (n=1,549) before the two check-ups.

CVD (I60-I69) for exclusion was defined by using an ICD-10 code based on claim data for KNHI.

The overall flow for patient enrollment is illustrated in Figure 1.

Ethical Review of Study

This study was conducted under ethical standards. This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board/Ethics Committee of Sejong University. This study was approved by the SJU-HR-E-2020-014 institutional Review Board and Privacy Office as an exempt study with a waiver of informed consent. To protect patients' private information, the data were anonymized under confidentiality guidelines and informed consent from individual patients was waived.

Change in Cholesterol Levels

Serum cholesterol levels were measured after 8 hours of fasting. Both baseline and follow-up cholesterol levels during 2002-2015 period were classified into low (cholesterol <180 mg/dL), moderate (180 < cholesterol <240 mg/dL), and high (cholesterol > 240 mg/dL).

Participants were then divided into 9 categories (low-to-low, low-to-moderate, low-to-high, moderate-to-low, moderate-to-moderate, moderate-to-high, high-to-low, high-to-moderate, and high-to-high) based on the change in cholesterol level from the two health check-ups. Those who sustained the same cholesterol level from the two check-ups were labeled as the reference groups (low-to-low, moderate-to-moderate, and high-to-high) (Figure 2).

Cerebrovascular Disease Incidence (CVD) and Characteristics

To identify CVD incidence, hospital admission records between January 1, 2002, and December 31, 2015, were utilized. Hospitalizations lasting from 2 days or more with ICD-10 diagnoses related to CVD were defined as CVD events; hemorrhagic infarction (I60, I61, I62), Ischemic infarction (I63, I64), Occlusion and stenosis (I65, I66) were included as ICD-10 diagnoses related to CVD.

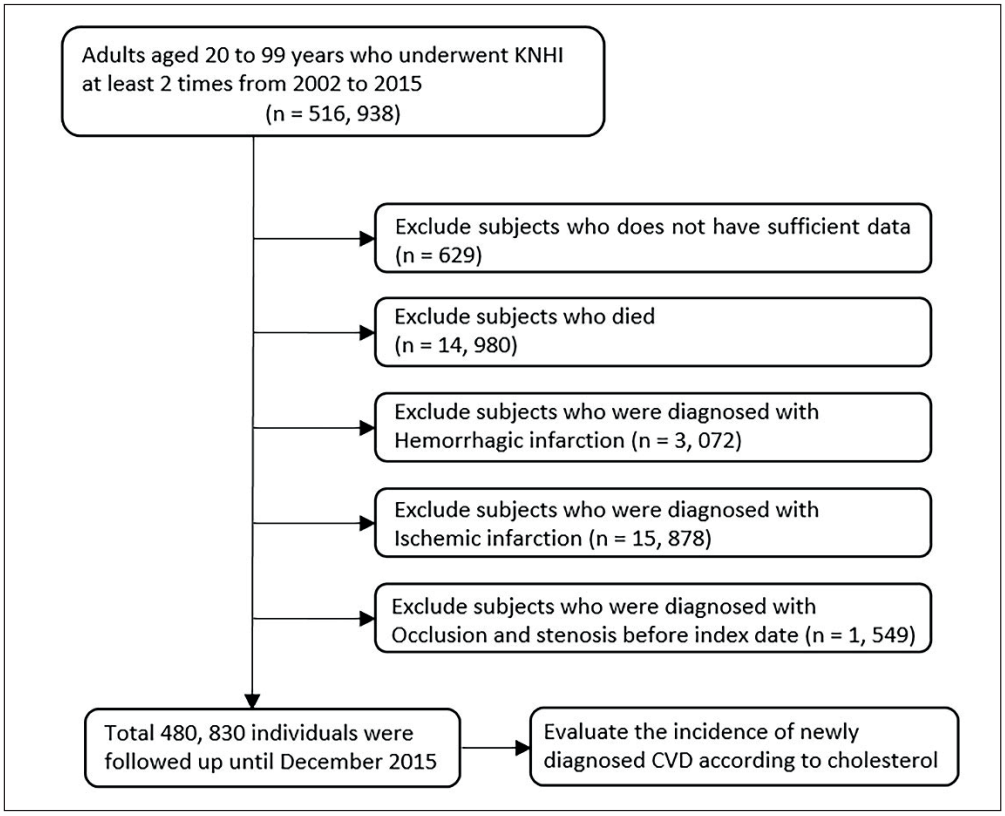

Figure 1. Flow chart of the selection of study population.

Participants were divided into 6 groups of age, 20-to-29, 30-to-39, 40-to-49, 50-to-59, 60-to-69, and 70-and-above. Body mass index (BMI) was calculated weight (kg) divided by height (m) squared. BMI was classified into categories of <18.5, 18.5 to 22.9, 23.0 to 24.9, and > 25.0 kg/m^2. Physical activity was classified into none, 1-2 per week, 3-4 per week, and 5-7 per week). Participants were classified into never, former, and current smokers regarding the smoking history

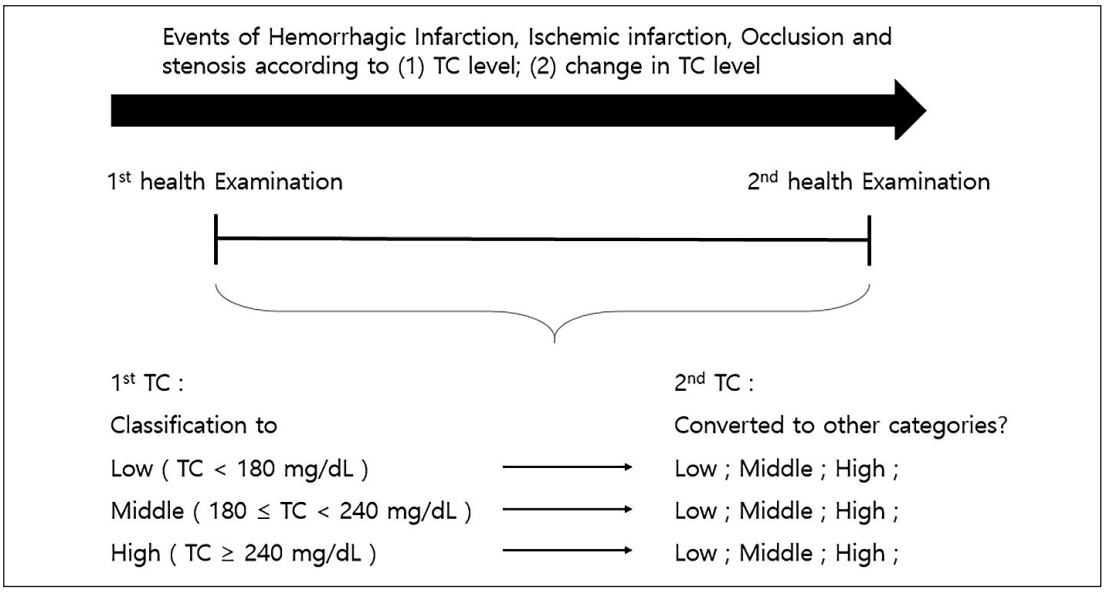

Figure 2. Diagram of comparison from first to second health exam based on TC level and TC change.

and were classified into none, 1 bottle per week, 2 bottles per week, and 3 bottles and more per week regarding alcohol use. Income status was grouped into 3 groups, 1st to 3rd, 4th to 7th, and 8th – 10th of 10th quarter. Comorbidities were determined by the Charlson comorbidity index (CCI) with ICD-10 diagnoses before the index date[22]. Aspirin and statin uses were indicated with a defined daily dose (DDD), which is the average maintenance dose per day to compare dosing of different aspirin/statins as standardized by the World Health Organization (WHO)[23]. The sum of defined daily dose for 3 years or more was used; people with aspirin or statin usage with 30 or more total defined daily doses were defined as aspirin or statin users. Hypertension history was defined as positive if there was physician diagnosis, anti-hypertensive medication usage, or blood pressure ≥ 140/90 mmHg. Diabetes history was defined positive if there was physician diagnosis, oral hypoglycemic agents or insulin usage, or fasting blood sugar (FBG) ≥ 126 mg/dL.

Statistical Analysis

Cox proportional hazards regression analysis was used to assess the risk of CVD with cholesterol level change. In Model 1, hazard ratios were adjusted for age and sex. In Model 2, hazard ratios were adjusted for age, sex, lifestyle variables (BMI, physical activity, smoking status, and alcohol consumption), socioeconomic factors (income status), and medical information (Charlson comorbidity index, aspirin, and statin medication, history of hypertension, diabetes mellitus, systolic blood pressure, and FBG level). Subgroup analyses stratified by age, sex, statin use, hypertension, and diabetes were also obtained. All statistical analyses were done in R software version 3.0.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Population Characteristics

The mean age of the participants was 42.4 years (SD 13.3). Males accounted for 50.7% of the participants. 192.1 mg/dL (SD 43.3) was the mean cholesterol level in the first health check-up (baseline). 190,808 (39.6%) participants had low cholesterol levels as a baseline and 241,319 (50.2%) participants and 48,703 (7.0%) had moderate and high cholesterol levels as baseline, respectively. People with high cholesterol were more likely to be older males with higher Charlson comorbidity index and fasting blood glucose; also they were more likely to have hypertension and diabetes and had higher aspirin and statin prescription rates (1.4% and 0.3%, respectively). People with low cholesterol group had more physical activities and less likely to smoke or drink (Table I).

Total Cholesterol and CVD Incidence and Hazard Ratios

10.3 years was the median period for CVD incidence. Higher cholesterol was correlated with ischemic infarction, occlusion, and stenosis but not with hemorrhagic infarction. Also, an increase in cholesterol level was correlated with CVD incidence but not with hemorrhagic infarction. In the unadjusted hazard ratio, higher hemorrhagic infarction was observed in moderate and high cholesterol groups compared to the low total cholesterol group (Unadjusted HR Model = 1.10; 95% confidence interval (CI) = 1.02-1.19, Unadjusted HR Model = 1.26; 95% CI = 1.12-1.43) but there was a statistical difference in hemorrhagic infarction risk for low, moderate, and high cholesterol groups when hazard ratio was adjusted.

Higher ischemic infarction risk was observed in the high cholesterol group (adjusted HR Model 1 [aHR1] = 1.29; 95% CI = 1.23-1.35, adjusted HR Model 2 [aHR2] = 1.46; 95% CI = 1.36-1.54) and the moderate cholesterol group (adjust HR Model 1 [aHR1] =1.11; 95% CI=1.07-1.15, adjust HR Model 2 [aHR2] =1.24; 95% CI=1.20-1.29) compared to the low cholesterol group.

Higher risks of occlusion and stenosis were found in the high cholesterol group (adjusted HR Model 1 [aHR1] = 1.55; 95% CI = 1.44-1.67, adjusted HR Model 2 [aHR2] = 1.62; 95% CI = 1.50-1.75) and the moderate cholesterol group (adjusted HR Model 1 [aHR1] = 1.19; 95% CI = 1.13-1.26, adjusted HR Model 2 [aHR2] = 1.28; 95% CI = 1.21-1.36) compared to the low cholesterol group (Table II).

CVD Incidence: Subgroup Analyses

The subgroup analysis stratified by characteristics including age, sex, aspirin, statin, hypertension, and diabetes demonstrated the CVD incidences by each stratified group. Women of the age of 20-29 years without hypertension, diabetes, or aspirin/statin use had the lowest CVD incidence. A change in cholesterol levels, either an increase or decrease, according to age were not associated with hemorrhagic/ischemic infarction, occlusion, or stenosis.

Table I. Baseline characteristics of study populations.

	Total	Baseline Total Cholesterol			*p*-value
		Low (TC < 180 mg/dL)	Moderate (180≤ TC <240 mg/dL)	High (TC ≥ 240 mg/dL)	
All subjects, n (%)	480,830	190,808 (39.6)	241,319 (50.2)	48,703 (10.1)	
Age, mean (SD)	42.4 (13.3)	38.8 (13.2)	43.9 (13.0)	48.4 (12.2)	<0.001
20 to 29	106,540 (22.1)	61,995 (32.4)	40,905 (16.9)	3,640 (7.4)	<0.001
30 to 39	90,651 (18.8)	38,257 (20.0)	45,032 (18.6)	7,362 (15.1)	
40 to 49	141,161 (29.3)	51,417 (26.9)	75,448 (31.2)	14,296 (29.3)	
50 to 59	82,068 (17.0)	21,748 (11.3)	46,517 (19.2)	13,803 (28.3)	
60 to 69	46,146 (9.5)	12,959 (6.7)	25,686 (10.6)	7,501 (15.4)	
≥70	14,264 (2.9)	4,432 (2.3)	7,731 (3.2)	2,101 (4.3)	
Sex, n (%)					
Male	244,243 (50.7)	95,001 (49.7)	124,794 (51.7)	24,448 (50.1)	<0.001
Female	236,587 (49.2)	95,807 (50.2)	116,525 (48.2)	24,255 (49.8)	
Baseline TC, mean (SD), mg/dL	192.1 (43.3)	157.5 (16.3)	204.5 (16.3)	266.3 (72.4)	<0.001
Body mass index, n (%), kg/m^2					
<18.5	21,279 (4.4)	12,978 (6.8)	7,675 (3.1)	626 (1.2)	<0.001
18.5 to 22.9	199,959 (41.5)	96,466 (50.5)	90,762 (37.6)	12,731 (26.1)	
23.0 to 24.9	112,170 (23.3)	39,670 (20.7)	59,899 (24.8)	12,601 (25.8)	
≥25.0	147,383 (30.6)	41,676 (21.8)	82,965 (34.3)	22,742 (46.6)	
N/A	39 (0.0)	18 (0.0)	18 (0.0)	3 (0.0)	
Physical activity, n (%), times per week					
None	235,898 (49.0)	93,359 (48.9)	118,049 (48.9)	24,490 (50.2)	<0.001
1 to 2	119,092 (24.7)	47,091 (24.6)	59,973 (24.8)	12,028 (24.6)	
3 to 4	58,269 (12.1)	22,805 (11.9)	29,791 (12.3)	5,673 (11.6)	
5 to 7	66,925 (13.8)	27,270 (14.2)	33,199 (13.6)	6,456 (13.2)	
N/A	646 (0.1)	283 (0.1)	307 (0.1)	56 (0.1)	
Smoking status, n (%)					
Never	312,825 (65.0)	125,528 (65.7)	156,040 (64.6)	31,257 (64.1)	<0.001
Former	40,213 (8.3)	14,475 (7.5)	21,164 (8.7)	4,574 (9.3)	
Current	127,517 (26.5)	50,684 (26.5)	63,991 (26.5)	12,842 (26.3)	
N/A	275 (0.0)	121 (0.0)	124 (0.0)	30 (0.0)	
Drinking, n (%), bottles (Soju) per week					
0	276,829 (57.5)	109,915 (57.6)	138,737 (57.4)	28,177 (57.8)	<0.001
1	50,372 (10.4)	21,604 (11.3)	24,471 (10.1)	4,297 (8.8)	
2	59,026 (12.2)	23,512 (12.3)	29,740 (12.3)	5,774 (11.8)	
≥3	45,912 (9.4)	16,758 (8.7)	24,020 (9.9)	5,134 (10.5)	
N/A	48,691 (10.1)	19,019 (9.9)	24,351 (10.0)	5,321 (10.9)	
Income status, n (%)					
1 to 3	134,149 (27.7)	58,553 (30.5)	63,550 (26.2)	12,046 (24.6)	<0.001
4 to 7	194,968 (40.3)	79,081 (41.3)	96,727 (40.0)	19,160 (39.0)	
8 to 10	140,038 (29.0)	47,854 (24.9)	75,646 (31.2)	1,6538 (33.8)	
N/A	11,675 (2.4)	5,320 (2.7)	5,396 (2.2)	959 (1.9)	
Charlson comorbidity index, n (%)					
0	181,594 (37.7)	75,872 (39.7)	89,458 (37.0)	16,264 (33.3)	<0.001
1	121,885 (25.3)	49,090 (25.7)	60,811 (25.1)	11,984 (24.6)	
2	76,029 (15.8)	29,074 (15.2)	38,751 (16.0)	8,204 (16.8)	
≥ 3	74,516 (15.3)	26,332 (13.4)	17,539 (15.7)	9,585 (19.3)	
N/A	26,806 (5.5)	10,440 (5.4)	13,700 (5.6)	2,666 (5.4)	
Aspirin medication, n (%)					
No	475,592 (98.9)	188,873 (98.9)	238,738 (98.9)	47,981 (98.5)	<0.001
Yes	5,238 (1.0)	1,935 (1.0)	2,581 (1.0)	722 (1.4)	
Statin medication, n (%)					
No	479,684 (99.7)	190,371 (99.7)	240,787 (99.7)	48,526 (99.6)	<0.001
Yes	1,146 (0.2)	437 (0.2)	532 (0.2)	177 (0.3)	
Hypertension, n (%)					
No	451,670 (93.9)	181,975 (95.3)	225,417 (93.4)	44,278 (90.9)	<0.001
Yes	29,160 (6.0)	8,833 (4.6)	15,902 (6.5)	4,425 (9.0)	
Systolic blood pressure, mean (SD), mm Hg	121.9 (16.1)	119.1 (15.1)	123.1 (16.2)	127.3 (17.1)	<0.001
Diabetes mellitus, n (%)					
No	46,8017 (97.3)	186,015 (97.4)	234,947 (97.3)	47,055 (96.6)	<0.001
Yes	12,813 (2.6)	4,793 (2.5)	6,372 (2.6)	1,648 (3.3)	
Fasting blood glucose, mean (SD), mg/dL	94.5 (25.9)	91.6 (23.0)	95.3 (24.7)	102.0 (37.7)	<0.001

Table II. Hazard ratios and incidence of hemorrhagic infarction, ischemic infarction, occlusion and stenosis by total cholesterol level.

Baseline TC	Low (TC <180 mg/dL)	Moderate (180≤ TC <240 mg/dL)	*p*-value	High (TC ≥ 240 mg/dL)	*p*-value
Number of people	190,808		241,319		48,703
Hemorrhagic infarction					
Cases	1,029	1,494		354	
Incidence rates[a] (mean)	0.59 (9.10)	0.66 (9.03)		0.76 (9.09)	
Unadjusted HR (95% CI)	1.00	1.10 (1.02-1.19)	0.013	1.26 (1.12-1.43)	0.0001
Model 1 aHR (95% CI)	1.00	0.98 (0.90-1.06)	0.637	1.02 (0.90-1.15)	0.731
Model 2 aHR (95% CI)	1.00	1.00 (0.91-1.09)	0.970	1.07 (0.94-1.22)	0.283
Ischemic infarction					
Cases	4,749	9,004		2,648	
Incidence rates[a] (mean)	2.76 (9.35)	4.04 (9.24)		5.82 (9.32)	
Unadjusted HR (95% CI)	1.00	1.45 (1.40-1.50)	<0.001	2.08 (1.98-2.18)	<0.001
Model 1 aHR (95% CI)	1.00	1.11 (1.07-1.15)	<0.001	1.29 (1.23-1.35)	<0.001
Model 2 aHR (95% CI)	1.00	1.24 (1.20-1.29)	<0.001	1.46 (1.39-1.54)	<0.001
Occlusion and stenosis					
Cases	1,851	3,666		1,170	
Incidence rates[a] (mean)	1.07 (9.50)	1.63 (9.34)		2.54 (9.46)	
Unadjusted HR (95% CI)	1.00	1.50 (1.42-1.59)	<0.001	2.32 (2.16-2.50)	<0.001
Model 1 aHR (95% CI)	1.00	1.19 (1.13-1.26)	<0.001	1.55 (1.44-1.67)	<0.001
Model 2 aHR (95% CI)	1.00	1.28 (1.21-1.36)	<0.001	1.62 (1.50-1.75)	<0.001

[a]Case per 1,000 person-years
Model 1: hazard ratio calculated by Cox proportional hazards regression adjusted for age and sex.
Model 2: additionally, adjusted for body mass index, Charlson comorbidity index, aspirin medication, statin medication, alcohol consumption, smoking habit, physical activity, income status, hypertension, diabetes, blood pressure and fasting serum glucose.
Acronyms: TC, total cholesterol; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

An increase in cholesterol levels in all age groups conferred more risk of ischemic infarction (aHR1 = 1.42; 95% CI=1.20-1.67 and, aHR2 = 1.28; 95% CI=1.08-1.52 in the low-high group for ischemic infarction), and occlusion and stenosis (aHR1 = 1.86; 95% CI=1.46-2.36 and aHR2 = 1.74; 95% CI=1.36-2.23 in the low-high group for occlusion and stenosis). Decreased cholesterol levels were not associated with reduced CVD in the entire study population.

However, in the age group 40-49, decreased cholesterol was associated with reduced CVD incidence. A decrease in cholesterol levels from low and moderate cholesterol baseline levels was both associated with less CVD risk in the entire study population. Decreased cholesterol levels from high cholesterol levels were not associated with lower hemorrhagic infarction, ischemic infarction, stenosis, or occlusion in both statin users and non-statin users. However, the group who changed from high to moderate cholesterol levels tended to have higher ischemic infarction, occlusion, and stenosis (Table III).

Subgroup Analysis and Hazard Ratio for CVD

Two models were applied for calculating the hazard ratio for CVD. The first model (Model 1) was the model adjusted from age and sex. Another model (Model 2) was adjusted from not just age and sex but also other variables including body mass index, Charlson comorbidity index, aspirin/statin usage, alcohol usage/smoking, physical activity, income status, hypertension, diabetes, blood pressure, and fasting serum glucose.

An increase in cholesterol levels to the high level was associated with more CVD risk except hemorrhagic infarction. (aHR1 = 1.11; 95% CI =1.04-1.17 and aHR2 = 1.14; 95% CI=1.07-1.2 in the low-to-moderate group for ischemic infarction); (aHR1 = 1.18; 95% CI =1.07-1.29 and aHR2 = 1.20; 95% CI=1.08-1.32 in the low-to-moderate group for occlusion and stenosis); (aHR1 = 1.42; 95% CI =1.20-1.67 and aHR2 = 1.28; 95% CI=1.08-1.52 in the low-to-high group for ischemic infarction); (aHR1 = 1.86; 95% CI =1.46-2.36 and aHR2 = 1.74; 95% CI=1.36-2.23 in the low-to-high group for occlusion/stenosis).

Table III. Characteristics of study population by change of total cholesterol level and incidence of hemorrhagic infarction, ischemic infarction, and occlusion and stenosis.

Baseline TC / Follow-up TC	Low (TC < 180 mg/dL)			Moderate (180≤ TC <240 mg/dL)			High (TC ≥ 240 mg/dL)		
	Low	Middle	High	Low	Middle	High	Low	Middle	High
Number of people	123,580	64,149	3,079	53,876	160,898	26,545	4,144	23,557	21,002
Hemorrhagic infarction									
Age									
20-29	112 (0.29)	28 (0.20)	1 (0.3)	25 (0.26)	55 (0.24)	1 (0.04)	0 (0)	7 (0.43)	2 (0.15)
30-39	86 (0.34)	38 (0.31)	3 (0.69)	34 (0.33)	107 (0.35)	13 (0.31)	0 (0)	8 (0.22)	17 (0.50)
40-49	166 (0.59)	118 (0.66)	7 (0.74)	84 (0.58)	270 (0.57)	45 (0.56)	7 (0.75)	42 (0.64)	28 (0.48)
50-59	105 (0.94)	72 (0.85)	8 (1.26)	97 (1.11)	233 (0.80)	51 (0.83)	14 (1.28)	47 (0.75)	57 (1.03)
60-69	132 (1.82)	68 (1.43)	11 (3.15)	81 (1.42)	202 (1.26)	44 (1.40)	12 (1.54)	42 (1.17)	36 (1.22)
≥ 70	42 (1.79)	30 (2.06)	2 (2.13)	43 (2.51)	95 (2.15)	14 (1.64)	4 (1.75)	19 (1.97)	12 (1.64)
Sex									
Men	373 (0.64)	182 (0.60)	6 (0.47)	192 (0.71)	490 (0.60)	69 (0.56)	18 (1.02)	79 (0.66)	75 (0.72)
Women	270 (0.50)	172 (0.60)	26 (1.59)	172 (0.73)	472 (0.70)	99 (0.79)	19 (0.94)	86 (0.80)	77 (0.82)
Aspirin medication									
No	628 (0.57)	348 (0.60)	32 (1.12)	356 (0.71)	937 (0.63)	164 (0.67)	35 (0.96)	158 (0.71)	147 (0.75)
Yes	15 (1.44)	6 (1.07)	0 (0)	8 (1.12)	25 (1.72)	4 (1.49)	2 (1.42)	7 (2.04)	5 (2.32)
Statin medication									
No	640 (0.57)	353 (0.60)	32 (1.11)	364 (0.72)	958 (0.64)	166 (0.67)	36 (0.96)	165 (0.73)	152 (0.77)
Yes	3 (1.25)	1 (0.99)	0 (0)	0 (0)	4 (1.71)	2 (2.37)	1 (4.56)	0 (0)	0 (0)
Hypertension									
No	586 (0.54)	323 (0.58)	25 (0.94)	309 (0.65)	851 (0.60)	147 (0.64)	30 (0.94)	139 (0.67)	134 (0.73)
Yes	57 (1.43)	31 (1.12)	7 (2.99)	55 (1.64)	111 (1.31)	21 (1.24)	7 (1.19)	26 (1.36)	18 (1.31)
Diabetes									
No	612 (0.56)	341 (0.59)	29 (1.04)	341 (0.70)	932 (0.63)	163 (0.67)	34 (0.97)	160 (0.73)	146 (0.76)
Yes	31 (1.24)	13 (0.98)	3 (2.68)	23 (1.28)	30 (0.90)	5 (0.79)	3 (1.03)	5 (0.67)	6 (1.22)
Ischemic infarction									
Age									
20-29	91 (0.24)	45 (0.33)	2 (0.46)	20 (0.20)	56 (0.25)	9 (0.37)	0 (0)	6 (0.37)	9 (0.69)
30-39	172 (0.68)	93 (0.76)	8 (1.85)	91 (0.89)	254 (0.83)	37 (0.89)	10 (2.25)	35 (0.95)	36 (1.06)
40-49	569 (2.05)	394 (2.21)	32 (3.40)	342 (2.38)	1,056 (2.25)	205 (2.56)	43 (4.65)	182 (2.78)	174 (3.00)
50-59	588 (5.37)	445 (5.32)	42 (6.77)	578 (6.76)	1,577 (5.53)	368 (6.12)	93 (8.75)	381 (6.21)	310 (5.69)
60-69	855 (12.21)	597 (13.10)	43 (12.70)	756 (13.83)	1,856 (12.00)	402 (13.27)	120 (16.21)	470 (13.68)	379 (13.43)
≥ 70	447 (20.36)	303 (22.22)	23 (26.44)	368 (23.07)	872 (21.04)	157 (19.51)	60 (28.99)	183 (20.33)	157 (23.01)
Sex									
Men	1,497 (2.60)	868 (2.91)	50 (4.00)	1,068 (4.00)	2675 (3.28)	464 (3.77)	129 (7.51)	471 (3.98)	375 (3.64)
Women	1,225 (2.28)	1,009 (3.56)	100 (6.23)	1,087 (4.67)	2,996 (4.47)	714 (5.70)	197 (10.04)	786 (7.49)	690 (7.56)

Continued

Table III *(continued)*. Characteristics of study population by change of total cholesterol level and incidence of hemorrhagic infarction, ischemic infarction, and occlusion and stenosis.

Baseline TC / Follow-up TC	Low (TC < 180 mg/dL)			Moderate (180≤ TC <240 mg/dL)			High (TC ≥ 240 mg/dL)		
	Low	Middle	High	Low	Middle	High	Low	Middle	High
Aspirin medication									
No	2,577 (2.34)	1,793 (3.11)	144 (5.13)	2,052 (4.17)	5482 (3.73)	1132 (4.61)	310 (8.75)	1250 (5.47)	1,031 (5.36)
Yes	145 (14.54)	84 (15.73)	6 (12.83)	103 (15.19)	189 (13.58)	46 (17.19)	16 (11.83)	52 (15.90)	34 (16.60)
Statin medication									
No	2,689 (2.42)	1,867 (3.22)	146 (5.15)	2,138 (4.29)	5,643 (3.81)	1,163 (4.70)	320 (8.74)	1,251 (5.61)	1,056 (5.45)
Yes	33 (14.41)	10 (10.00)	4 (18.19)	17 (14.08)	28 (12.48)	15 (17.77)	6 (30.05)	6 (8.72)	9 (14.46)
Hypertension									
No	2,199 (2.05)	1,524 (2.75)	120 (4.56)	1,686 (3.61)	4,672 (3.33)	974 (4.26)	236 (7.55)	1,008 (4.92)	903 (4.98)
Yes	523 (13.71)	353 (13.27)	30 (13.30)	469 (14.70)	999 (12.23)	204 (12.48)	90 (16.20)	249 (13.56)	162 (12.22)
Diabetes									
No	2,415 (2.22)	1,723 (3.03)	141 (5.13)	1,936 (4.02)	5,291 (3.64)	1,094 (4.58)	285 (8.37)	1,178 (5.45)	995 (5.24)
Yes	307 (12.74)	154 (12.04)	9 (8.21)	219 (12.68)	380 (11.86)	84 (13.75)	41 (14.86)	79 (11.00)	70 (15.02)
Occlusion and stenosis									
Age									
20-29	32 (0.08)	22 (0.16)	0 (0)	11 (0.11)	18 (0.08)	4 (0.16)	0 (0)	6 (0.37)	7 (0.53)
30-39	80 (0.32)	49 (0.40)	2 (0.46)	42 (0.41)	111 (0.36)	31 (0.74)	1 (0.22)	25 (0.68)	26 (0.77)
40-49	237 (0.85)	198 (1.11)	13 (1.37)	160 (1.11)	499 (1.06)	104 (1.29)	19 (2.03)	99 (1.50)	87 (1.49)
50-59	275 (2.48)	199 (2.35)	30 (4.78)	259 (2.98)	745 (2.58)	166 (2.73)	48 (4.44)	190 (3.06)	172 (3.12)
60-69	289 (4.00)	198 (4.21)	22 (6.34)	285 (5.05)	685 (4.30)	134 (4.29)	62 (8.10)	168 (4.72)	144 (4.94)
≥ 70	122 (5.26)	79 (5.46)	4 (4.27)	112 (6.62)	236 (5.39)	64 (7.61)	14 (6.22)	55 (5.79)	47 (6.51)
Sex									
Men	578 (1.00)	361 (1.20)	26 (2.06)	488 (1.81)	1146 (1.40)	222 (1.80)	69 (3.95)	266 (2.23)	199 (1.92)
Women	457 (0.85)	384 (1.35)	45 (2.76)	381 (1.62)	1148 (1.70)	281 (2.24)	75 (3.73)	277 (2.59)	284 (3.06)
Aspirin medication									
No	972 (0.88)	722 (1.24)	68 (2.39)	820 (1.65)	2224 (1.50)	492 (2.00)	135 (3.73)	524 (2.35)	468 (2.41)
Yes	63 (6.12)	23 (4.12)	3 (6.18)	49 (6.99)	70 (4.86)	11 (4.11)	9 (6.48)	19 (5.59)	15 (7.07)
Statin medication									
No	1,028 (0.92)	742 (1.27)	69 (2.41)	858 (1.70)	2,279 (1.52)	501 (2.02)	142 (3.80)	538 (2.38)	476 (2.43)
Yes	7 (2.94)	3 (2.95)	2 (8.75)	11 (8.89)	15 (6.49)	2 (2.37)	2 (9.34)	5 (7.12)	7 (11.17)
Hypertension									
No	847 (0.78)	618 (1.11)	54 (2.03)	687 (1.46)	1,911 (1.35)	428 (1.86)	109 (3.43)	449 (2.17)	415 (2.27)
Yes	188 (4.77)	127 (4.61)	17 (7.37)	182 (5.49)	383 (4.55)	75 (4.45)	35 (6.07)	94 (4.94)	68 (5.00)
Diabetes									
No	892 (0.82)	680 (1.19)	69 (2.48)	753 (1.55)	2,102 (1.43)	475 (1.97)	121 (3.49)	499 (2.28)	450 (2.35)
Yes	143 (5.77)	65 (4.96)	2 (1.79)	116 (6.54)	192 (5.84)	28 (4.44)	23 (8.10)	44 (6.01)	33 (6.82)

Absolute cases with incidence rates (1,000 person-years) were noted.

Furthermore, in people with high cholesterol level as baseline, a decrease in cholesterol was not associated with decreased CVD; a change from high cholesterol to low cholesterol level was associated with higher ischemic infarction, occlusion and stenosis risk even with the decrease in cholesterol (Table IV).

The mean changes for each group were 13.87 (SD, 30.85), -1.87 (SD, 35.63), and -32.20 (SD, 84.04) in the low-, moderate-, and high-cholesterol group, respectively (Table V). The adjusted hazard ratio from the change of 1 and 2 standard deviations was carried out in the low-, moderate-, and high-colesterol groups. Finally, a change in cholesterol level did not influence hemorrhagic infarction. Moreover, the group that had cholesterol levels reduced by 2 standard deviations from high cholesterol levels did not demonstrate statistically significant reductions in ischemic infarction, occlusion, or stenosis. Importantly, a high risk for ischemic infarction, occlusion, and stenosis was observed in the rest of the group by the change of cholesterol level. (aHR=1.11; 95% CI 1.04-1.18 in low-, aHR=1.12; 95% CI=1.07-1.18 in moderate- and aHR=1.15; 95% CI=1.03-1.30 in high- cholesterol group per 1 SD [29.1 mg/dL] increase for ischemic infarction) (aHR=1.20; 95% CI 1.07-1.33 in low-, aHR=1.29; 95% CI=1.16-1.44 in moderate- and aHR=1.11; 95% CI=0.93-1.32 in high- cholesterol group per 2 SD [58.2 mg/dL] increase for ischemic infarction) (aHR=1.15; 95% CI 1.04-1.28 in low-, and aHR=1.08; 95% CI=1.00-1.17 in moderate- cholesterol group per 1 SD [29.1 mg/dL] increase for occlusion and stenosis). (aHR=1.30; 95% CI 1.10-1.54 in low-, and aHR=1.24; 95% CI=1.05-1.47 in moderate- cholesterol group per 2 SD [58.2 mg/dL] increase for ischemic infarction) (Table V).

Discussion

While it was found that low cholesterol level at baseline correlates with a lower risk of stroke compared to moderate/high cholesterol level which is consistent with prior findings suggesting a higher risk of stroke with higher cholesterol[9,10,17,24], our result indicates that a decrease in cholesterol level may not correlate with a decreased risk of stroke and may even be associated with a higher risk of stroke. Our findings showed that low to high cholesterol level on both Model 1 and 2 is associated with more hemorrhagic stroke. Also, it is demonstrated that low to moderate or high cholesterol levels, as well as moderate to a high level of cholesterol, are associated with more ischemic stroke and occlusion/stenosis in both models. Such discoveries are consistent with prior findings from the relationship between cholesterol level and cardiovascular disease risk[18,19,24]. However, our study also found that a change from moderate to low cholesterol levels correlates with more hemorrhagic and ischemic stroke and occlusion/stenosis on Model 1 and that a change from high to low cholesterol levels correlates with more ischemic stroke on both models and more occlusion/stenosis on Model 1; those findings would contradict previous findings from cardiovascular disease risk and cholesterol level.

For ischemic stroke and occlusion/stenosis, there have been multiple studies[24-26] that demonstrated an association between LDL and total cholesterol level and ischemic stroke risk and there have been findings[27,28] that showed an association between LDL level and total cholesterol level which are in line with the increase in ischemic stroke after an increase in total cholesterol from low to moderate/high total cholesterol level in this study. For the trend of increasing ischemic stroke and occlusion/stenosis after a decrease in total cholesterol level, the variability of cholesterol level from such decreases may have accounted for the increased incidence of ischemic stroke and occlusion/stenosis. There have been researches demonstrating that more variabilities in total cholesterol level, as well as HDL and LDL levels, are associated with more ischemic stroke and occlusion/stenosis[29-31]. Such variabilities in cholesterol level may lead to more crystallization and dissolution of cholesterol in vessel plaques leading to plaque rupture and more atheroma formation; all of those can lead to increased risk of stroke and occlusion/stenosis[32,33]. Furthermore, LDL variability correlates with lower cerebral blood flow leading to stenosis/occlusion and ischemic stroke[34], and cholesterol variabilities are associated with conditions leading to more ischemic stroke such as frailty[35]. With such a positive association between cholesterol variability and ischemic stroke and occlusion/stenosis, the finding where a decrease in total cholesterol is associated with more ischemic stroke and occlusion/stenosis may be explained.

For hemorrhagic stroke, there have been findings[36-39] where less cholesterol level is associated with more hemorrhagic stroke just as in the finding from this study where hemorrhagic stroke increased in Model 1 when cholesterol level decreased from moderate to low. Such an inverse relationship between total cholesterol level and hemorrhagic stroke may be explained by biological mechanisms.

Table IV. Hazard ratios of hemorrhagic infarction, ischemic infarction, occlusion and stenosis by total cholesterol level change.

Baseline TC / Follow-up TC	Low (TC < 180 mg/dL)			Moderate (180≤ TC <240 mg/dL)			High (TC ≥ 240 mg/dL)		
	Low	Middle	High	Low	Middle	High	Low	Middle	High
Change, mg/dL, mean (SD)	1.2 (18.2)	34.0 (19.2)	102.3 (124.2)	-34.4 (20.3)	1.2 (19.6)	45.5 (62.8)	-112.8 (117.1)	-47.5 (79.0)	0.9 (63.5)
Number of people (%)	123,580 (64.8)	64,149 (33.6)	3 079 (1.6)	53,876 (22.3)	160,898 (66.7)	26,545 (11.0)	4,144 (8.5)	23,557 (48.4)	21,002 (43.1)
Hemorrhagic Infarction									
Case, n	643	354	32	364	962	168	37	165	152
Incidence rates	0.57	0.60	1.10	0.72	0.64	0.68	0.98	0.73	0.77
Model 1									
aHR	1.00	0.97	1.59	1.14	1.00	1.10	0.95	0.93	1.00
95% CI		0.85 to 1.10	1.12 to 2.28	1.01 to 1.28		0.85 to 1.18	0.77 to 1.39	0.75 to 1.16	
p-value		0.6308	0.0102	0.0081		0.0098	0.0223	0.0333	
Model 2									
aHR	1.00	0.98	1.56	1.11	1.00	1.01	0.95	0.90	1.00
95% CI		0.85 to 1.12	1.07 to 2.25	0.97 to 1.26		0.82 to 1.16	0.64 to 1.40	0.72 to 1.14	
p-value		0.7363	0.0192	0.0277		0.0385	0.0482	0.0380	
Ischemic Infarction									
Case, n	2722	1877	150	2155	5671	1178	326	1257	1065
Incidence rates	2.44	3.22	5.25	4.30	3.81	4.79	8.80	5.60	5.45
Model 1									
aHR	1.00	1.11	1.42	1.15	1.00	1.12	1.51	1.01	1.00
95% CI		1.04 to 1.17	1.20 to 1.67	1.09 to 1.21		1.05 to 1.20	1.33 to 1.71	0.93 to 1.10	
p-value		0.0008	< 0.0001	< 0.0001		0.0005	< 0.0001	0.879	
Model 2									
aHR	1.00	1.14	1.28	1.05	1.00	1.10	1.20	0.97	1.00
95% CI		1.07 to 1.21	1.08 to 1.52	1.00 to 1.11		1.03 to 1.17	1.05 to 1.36	0.89 to 1.05	
p-value		< 0.0001	0.0052	0.0069		0.0057	0.0057	0.4442	
Occlusion and stenosis									
Case, n	1035	745	71	869	2294	503	144	543	483
Incidence rates	0.92	1.26	2.42	1.71	1.53	2.02	3.84	2.38	2.44
Model 1									
aHR	1.00	1.18	1.86	1.14	1.00	1.21	1.50	0.95	1.00
95% CI		1.07 to 1.29	1.46 to 2.36	1.05 to 1.23		1.10 to 1.33	1.24 to 1.81	0.84 to 1.08	
p-value		0.0007	< 0.0001	0.0013		0.0001	< 0.0001	0.420	
Model 2									
aHR	1.00	1.20	1.74	1.04	1.00	1.19	1.20	0.95	1.00
95% CI		1.08 to 1.32	1.36 to 2.23	0.96 to 1.13		1.08 to 1.32	0.98 to 1.46	0.83 to 1.08	
p-value		0.0004	< 0.0001	0.03109		0.0006	0.00764	0.4150	

Model 1 : adjusted for age and sex. Model 2 : additionally adjusted for body mass index, Charlson comorbidity index, statin medication, aspirin medication, alcohol consumption, smoking habit, physical activity, income status, hypertension, diabetes mellitus, blood pressure and fasting serum glucose. aHR indicates adjusted hazard ratio; CI, confidence interval; SD, standard deviation; TC, total cholesterol.

[a]Cases per 1000 person-years.

Table V. Hazard ratios of hemorrhagic infarction, ischemic infarction, occlusion and stenosis by total cholesterol level change as a continuous variable.

Baseline TC	Low	Moderate		High		
	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Mean Change of TC[a]	13.87 (30.85)		-1.87 (35.63)		-32.20 (84.04)	
Per 1 SD of change[b]						
hemorrhagic infarction	1.02 (0.88-1.18)	0.81	1.09 (0.96-1.24)	0.175	1.04 (0.74-1.46)	0.817
Ischemic infarction	1.11 (1.04-1.18)	0.002	1.12 (1.07-1.18)	<0.001	1.15 (1.03-1.30)	0.015
Occlusion and stenosis	1.15 (1.04-1.28)	0.0058	1.08 (1.00-1.17)	0.04	1.11 (0.93-1.32)	0.026
Per 2 SD of change[b]						
hemorrhagic infarction	1.12 (0.87-1.45)	0.385	1.17 (0.87-1.58)	0.304	1.16 (0.37-3.65)	0.801
Ischemic infarction	1.20 (1.07-1.33)	0.001	1.29 (1.16-1.44)	<0.001	1.10 (0.73-1.66)	0.636
Occlusion and stenosis	1.30 (1.10-1.54)	0.002	1.24 (1.05-1.47)	0.0122	0.75 (0.37-1.54)	0.438

Adjusted for age, sex, body mass index, Charlson comorbidity index, statin medication, alcohol consumption, smoking habit, physical activity, income status, hypertension, diabetes mellitus, blood pressure, and fasting serum glucose. CI indicates confidence interval; HR, hazard ratio; SD, standard deviation; TC, total cholesterol.
[a]Values are presented to mean (SD) mg/dL.
[b]1 SD of change was calculated as 29.1 mg/dL.

There have been scome scholars[40] demonstrating that high triglyceride levels can lead to prothrombotic states as factor VII and factor IX are positively correlated with triglyceride; therefore, low triglyceride levels would be more likely seen with low total cholesterol levels may lead to pro-hemorrhagic states. Also, as cholesterol is an essential component of cell membranes, there have been findings from animal studies[41,42] where low cholesterol levels cause endothelial weakness in intracerebral arteries, and it has been proposed that low cholesterol levels can lead to endothelium being more prone to damage and eventual rupture. For the finding in this study where hemorrhagic stroke increased when cholesterol level was increased from low level to high level in both models, it could be from increased variability of cholesterol rather than an increase in cholesterol itself. It has been found that high variability of HDL is associated with more hemorrhagic stroke[30]. Although we only looked at the total cholesterol level in this study, it may have been a change in HDL that could have contributed to more hemorrhagic stroke when cholesterol level increased from low to high because high variability in HDL is linked to more atheroma progression which makes vessels prone to hemorrhage[33].

Our study is not without limitations. First, the data from the national database are not collected exclusively for our study and thus it is difficult to determine which factors may have contributed to a change in cholesterol level. For instance, a decrease in cholesterol level may reflect poor health conditions that may have contributed to more stroke[43]. Second, the study does not have information on LDL, HDL, TG, or other specific cholesterol levels. While there are studies that demonstrated that LDL levels correlate with total cholesterol levels[27,28], changes in total cholesterol level may not necessarily correlate with changes in LDL and total cholesterol level. Also, its changes may not necessarily have a robust association with HDL, TG, and other specific cholesterol levels. Third, in this study, there was no specific information on details of statin used for the population. As there can be different dosages and different kinds of statins, a future study specifying details of statin usage by low, moderate, or high intensity may aid in evaluating the relationship between total cholesterol level and stroke.

Conclusions

Our study demonstrated that cholesterol changes from baseline, especially huge changes in the level such as low level to high level or high level to a low level, may lead to an increase in ischemic and hemorrhagic stroke. Such findings illustrate that total cholesterol variabilities may lead to more ischemic and hemorrhagic stroke. Further interventional studies are warranted to see if reductions in the variability of total cholesterol levels help control the risk of ischemic and hemorrhagic stroke.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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