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Impact of cumulative exposure and variations of small dense low-density lipoprotein cholesterol on the risk of incident cardiovascular diseases or stroke among middle-aged and old adults: Insights from CHARLS

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Abstract

Objection: This study aims to investigate the associations of cumulative small dense low-density lipoprotein cholesterol (sdLDL-C) and changes with cardiovascular disease (CVD) or stroke risk in middle-aged and old adults. *Methods:* Study data were extracted from the China Health and Retirement Longitudinal Study (CHARLS) database in 2011-2015. Associations of cumulative sdLDL-C, sdLDL-C change and sdLDL-C cluster (divided into 3 classes using the k-means cluster analysis) with risk of CVD or stroke were investigated utilizing multivariate logistic regression analysis, which evaluated through odds ratio (OR) with 95% confidence interval (CI). *Results:* Follow-up until 2020, 662 of 4,353 participants had CVD or stroke. After adjusting for selected covariates, compared to lower cumulative levels of sdLDL-C (≤82.2), cumulative sdLDL-C levels of (99.4, 120] (OR=1.44, 95%CI: 1.12-1.86) and >120 (OR=1.41, 95%CI: 1.09-1.82) were associated with increased CVD/stroke odds, respectively. Compared to persistent low sdLDL-C change levels, persistent middle, persistent high and increasing sdLDL-C change were all linked to increased odds of CVD/stroke (all $P<0.05$). Participants with sdLDL-C level of Class 2 and Class 3 had increased odds of CVD/stroke risk, compared to those with sdLDL-C level of Class 1 (all $P<0.05$). Similar associations were observed between sdLDL-C and CVD risk but not with stroke.
Conclusions: High cumulative sdLDL-C levels and stably high sdLDL-C change was associated with an increased CVD/stroke risk. Timely monitoring sdLDL-C change may play a pivotal role in mitigating disease incidence, and however, targeted interventions and the underlying mechanisms of these associations need further clarification.

Keywords: sdLDL-C; stroke; CVD; CHARLS

INTRODUCTION

Cardiovascular diseases (CVD) and stroke are the leading causes of death worldwide and result in grievous disease burden.[1,2] With the aging population, as well as the increasing prevalence of metabolic diseases, the incidence of CVDs is expected to keep rising.[3] In China, stroke has also emerged as an escalating public health challenge among middle-aged and old adults, remaining a leading cause of death and long-term disability.[4,5]

Pivotal modifiable factors identified for CVD prevention include health behaviors and health risk factors, such as cholesterol and blood pressure.[6] Of which, low-density lipoprotein cholesterol (LDL-C) is closely related to the occurrence and progression of cardiovascular and cerebrovascular diseases and is a key target for prevention efforts.[7] Neverthelss, recent studies emphasized that even when LDL-C levels are controlled within a reasonable range, cardiovascular and cerebrovascular related mortality risks still exist.[8,9]

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Notably, among different subfractions of LDL-C, the small dense LDL-C (sdLDL-C) exhibits distinct characteristics that are easier to be oxidized, permeable to the endothelium, and has a longer time for circulation than LDL-C with larger particle subfractions.[10] As a burgeoning risk factor, according to previous studies, sdLDL-C can predict the development of acute ischemic stroke and coronary heart disease better than LDL-C.[11,12] Existing studies often focus on single measurements instead of the role of sdLDL-C changes over time. In fact, a single assessment of sdLDL-C only provides a "snapshot" of lipid abnormality burden, which might not be enough for accurate risk assessment. Therefore, the effects of cumulative increases or changes of sdLDL-C on cardiovascular and cerebrovascular risk still be revealed later.

Herein, this study based on the China Health and Retirement Longitudinal Study (CHARLS) database, explored associations of sdLDL-C cumulative exposure and changes with stroke and CVD risk in Chinese population, with the aim of coming up with new strategies for long-term prevention and treatment of cardiovascular and cerebrovascular diseases in the community.

METHODS

Study design and participants

Data in this retrospective cohort study were extracted from the CHARLS database. The CHARLS is a nationally representative longitudinal survey of persons aged 45 years in China. Supported by the multistage probability sampling method, the CHARLS survey commenced in 2011, with follow-up evaluations occurring biennially, and by 2020, a total of five rounds had been completed.[13]

Initially, 16,197 middle-aged and old adults (≥45 years) were included. The exclusion criteria were (1) lost to follow-up in 2020; (2) missing information on key covariates; (3) having self-reported CVD or stroke events before 2015. The final sample size was 4,353 in this analysis (Fig. 1). Dataset used in this study is available for downloading at the CHARLS home website

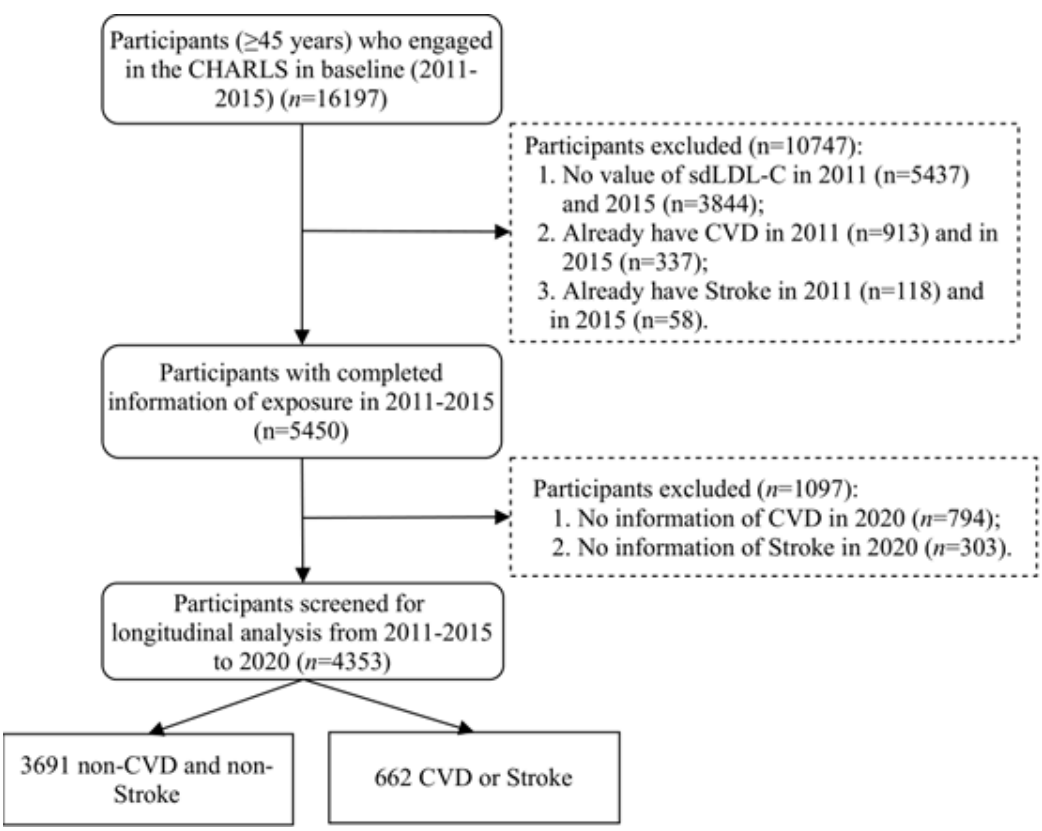

Figure 1. Flowchart of the study population.

(http://charls.pku.edu.cn/en). Ethical approval for the gathering of CHARLS data was obtained from the Biomedical Ethics Review Board of Peking University (IRB00001052-11015), and all participants have signed an informed consent form. Therefore, according to relevant regulations, the Institutional Review Board of our hospital has waived the ethical approval process for this study.

Cumulative levels and changes of sdLDL-C

Blood measurements from 2011 to 2012 were covered in CHARLS Wave 1, and those in 2015 were published in Wave 3. Therefore, the cumulative sdLDL-C was calculated through the expression: (sdLDL-C in wave 1 + sdLDL-C in wave 3) / 2 × period (2015 - 2012).[14] The cumulative sdLDL-C levels were further divided into four groups based on the quartile values, including ≤82.2 mg/dL, (82.2 mg/dL, 99.4], (99.4 mg/dL, 120] and >120 mg/dL.[15]

The sdLDL-C changes were the difference values between 2011 and 2015 of each participant. In this study, changes of sdLDL-C were divided into 5 groups, including persistent low, persistent middle, persistent high, decreasing, and increasing groups. Specifically, the persistent low group included participants with sdLDL-C levels of the 1st quartile in both 2011 and 2015, persistent middle group included those with sdLDL-C levels of the 2nd or 3rd quartile in both 2011 and 2015, and persistent high group included those with sdLDL-C levels of the 4th quartile in both 2011 and 2015. Individuals with sdLDL-C levels that moved from a higher quartile to a lower quartile between 2011 and 2015 were included in the decreasing group, and those with sdLDL-C levels that moved from a lower quartile to a higher quartile between 2011 and 2015 were included in the increasing group. Additionally, K-means cluster analysis was used to categorize sdLDL-C levels into 3 classes.

Diagnosis of CVD and stroke

The outcome events of this study were CVD and stroke. In the CHARLS database, the presence of CVD was determined through the question "Did your doctor tell you that you have been diagnosed with a heart attack, angina pectoris, coronary heart disease, heart failure, or other heart problem?" Similarly, the occurrence of stroke was ascertained by the question "Did your doctor tell you that you were diagnosed with a stroke?".

Definitions of covariates

Variables as potential confounding factors were included at baseline. Demographic covariates included age (years), gender, education level, annual income (yuan) and place of residence. Health behavior information included smoking status, drinking status, physical activity (MET·min/week) and body mass index (BMI, kg/cm^2). Laboratory examination included C-reactive protein (CRP, mg/L) and uric acid (UA, mg/dL). Complication and drug therapy status included hypertension, dyslipidemia, diabetes mellitus (DM), cancer, chronic lung diseases, liver disease, chronic kidney disease (CKD) and antihyperlipidemic drug use.

Statistical analysis

Continuous data were described using mean and standard deviation (Mean ± SD), and the Kruskal-Wallis rank sum test was used for comparation between groups. Categorical data were presented through frequency and proportion [N (%)], and Chi-square test (χ^2) or Fisher exact probability test was utilized for the comparation.

Covariables were selected using a two-step method. A univariate logistic regression model was first established to identify variables significantly associated with outcomes, and then, bidirectional stepwise regression was used to select the final covariates among the above variables. Multivariate logistic regressions were used to explore the associations of cumulative levels and changes of sdLDL-C with CVD/stroke in middle-aged and old adults, which were evaluated through odds ratios (ORs) with 95% confidence intervals (CIs). In addition, the restricted cubic spline (RCS) curves were drawn to reflect association trends between cumulative sdLDL-C and CVD or stroke. In all calculations, a two-sided P-value<0.05 was required for statistical significance.

K-means cluster analysis was conducted using the "stats" Package (R version 4.2.3), and its visualization was based on the "factoextra" Package (R version 1.0.7). RCS curve plotting was drawn utilizing the "rcssci" Package (R version 0.4.0). Variables with missing values were shown in Table S1. Template method (R Package "VIM") and multiple interpolation method (R Package "mice") were used to process the missing data. The sensitivity analysis before and after imputation of missing data was shown in Table S2.

RESULTS

Characteristics of participants

A total of 4,353 eligible participants were included in this study and 662 eventually developed CVD or stroke. As shown in Table 1, the average age of total population was 59.29 years old, and 44.96% of them were males. Regarding complications, the proportions of participants with CVD or stroke were significantly higher than those without CVD or stroke, including hypertension (60.57% vs. 46.60%), dyslipidemia (71.30% vs. 62.10%), DM (17.67% vs. 14.28%), chronic lung diseases (11.33% vs. 7.10%), liver disease (4.38% vs. 2.71%), CKD (6.34% vs. 4.09%) and antihyperlipidemic drug (6.50% vs. 2.93%). The median CRP level in non-CVD/stroke group was significantly lower than that in CVD/stroke group (0.89 mg/L vs. 1.22 mg/L). The number of individuals with BMI level of ≥24 kg/cm^2 was significantly larger in CVD/stroke group than that in non-CVD/stroke group (43.05% vs. 33.73%).

K-means cluster analysis categorized the study population into three classes based on sdLDL-C levels from 2011 to 2015 (Figure 2a and 2b). Figure 2c showed that individuals in Class 1 (N=1859) had average sdLDL-C levels of 26.07 mg/dL in 2011 and of 25.86 mg/dL in 2015, indicating a trend of consistently low sdLDL-C levels. Class 2 (N=1838) had an average sdLDL-C level of 37.26 mg/dL in 2011 and 36.65 mg/dL in 2015, reflecting these participants had sdLDL-C at a moderate level. People in Class 3 (N=656) had an average sdLDL-C level of 52.71 mg/dL in 2011 and 48.75 mg/dL in 2015, reflecting higher-than-average sdLDL-C levels. Additionally, each class exhibited a roughly normal distribution of sdLDL-C levels (Figure 2d).

Screening for covariates associated with CVD/stroke

The bidirectional stepwise method was used to establish a logistic regression model for selecting potential confounding factors related to the risk of CVD or stroke (Table S3). In CVD or stroke model (Akaike Information Criterion [AIC]=3619.19), the selected covariates included age, gender, hypertension, chronic lung diseases, liver disease, CKD, antihyperlipidemic drug, smoking, and BMI (a total of 9). These variables were selected as covariates and further included in the adjustment of multivariable model. Besides, we established regression models between variables and CVD-only and stroke-only, respectively, and the selected covariates were adjusted in analysis on associations of sdLDL-C with CVD and stroke, respectively.

Associations of sdLDL-C levels and changes with the risk of CVD or stroke

Associations of cumulative sdLDL-C, sdLDL-C change and clustered sdLDL-C groups with new-onset CVD or stroke in 2020 were further evaluated. According to Table 2, after adjusting for selected covariates, compared to lower cumulative levels of sdLDL-C (≤82.2 mg/dL), cumulative sdLDL-C levels of (99.4 mg/dL, 120] (OR=1.44, 95%CI: 1.12-1.86, *P*=0.005) and >120 mg/dL (OR=1.41, 95%CI: 1.09-1.82, *P*=0.010) were associated with increased odds of CVD or stroke among middle-aged and olde adults, respectively. Compared to persistent low levels of sdLDL-C change, persistent middle (OR=1.56, 95%CI: 1.12-2.21, *P*=0.010), persistent high (OR=1.62, 95%CI: 1.14-2.32, *P*=0.008) and increasing (OR=1.56, 95%CI: 1.14-2.17, *P*=0.006) sdLDL-C change from 2011 to 2015 were all linked to increased odds of CVD/stroke. Additionally, compared with participants with sdLDL-C level of Class 1, those with sdLDL-C level of Class 2 (OR=1.25, 95%CI: 1.03-1.52, *P*=0.022) and Class 3 (OR=1.46, 95%CI: 1.14-1.88, *P*=0.003) had increased odds of CVD/stroke risk, respectively.

Associations of sdLDL-C with CVD and stroke

Furthermore, we assessed the associations of cumulative sdLDL-C, sdLDL-C change and clustered sdLDL-C with CVD and stroke, respectively. As presented in Table S4, significant associations of high cumulative sdLDL-C, persistent middle/high/increasing sdLDL-C change, as well as sdLDL-C level of Class 2 and 3 with increased CVD risk were observed (all *P*<0.05). However, only the association between cumulative sdLDL-C level of (82.2 mg/dL, 99.4] and stroke (OR=1.56, 95%CI: 1.04-2.37, *P*=0.032), as well as between increasing sdLDL-C change and stroke (OR=1.66, 95%CI: 1.02-2.82, *P*=0.049) was significant, respectively (Table S5).

Similarly, the RCS curve further showed that there were linear associations of the cumulative levels of sdLDL-C from 2011 to 2015 with the onset risk of CVD/stroke and CVD in the middle-aged and old adults (Figure 3a and 3b). No linear or non-linear association has been observed

Table 1: Characteristics of participants in CVD/stroke group and non-CVD/stroke group

Variables	Total (N=4353)	Non-CVD/stroke (N=3691)	CVD/stroke (N=662)	Statistics	P
Age, years, Mean (±SD)	57.77 (±8.31)	57.50 (±8.36)	59.29 (±7.85)	t' = -5.346	<0.001
Gender, n (%)				$\chi2$ = 2.914	0.088
Male	1957 (44.96)	1680 (45.52)	277 (41.84)		
Female	2396 (55.04)	2011 (54.48)	385 (58.16)		
Education level, n (%)				$\chi2$ = 4.733	0.094
No formal education	1185 (27.22)	992 (26.88)	193 (29.15)		
Primary school	1803 (41.42)	1518 (41.13)	285 (43.05)		
Middle school or above	1365 (31.36)	1181 (32.00)	184 (27.79)		
Annual income, yuan, n (%)				$\chi2$ = 1.221	0.543
<10000	748 (17.18)	631 (17.10)	117 (17.67)		
≥10000	721 (16.56)	621 (16.82)	100 (15.11)		
Unknown	2884 (66.25)	2439 (66.08)	445 (67.22)		
Place of residence, n (%)				$\chi2$ = 0.299	0.584
Rural village	2909 (66.83)	2460 (66.65)	449 (67.82)		
Urban community	1444 (33.17)	1231 (33.35)	213 (32.18)		
Hypertension, n (%)				$\chi2$ = 43.317	<0.001
No	2232 (51.27)	1971 (53.40)	261 (39.43)		
Yes	2121 (48.73)	1720 (46.60)	401 (60.57)		
Dyslipidemia, n (%)				$\chi2$ = 20.112	<0.001
No	1589 (36.50)	1399 (37.90)	190 (28.70)		
Yes	2764 (63.50)	2292 (62.10)	472 (71.30)		
DM, n (%)				$\chi2$ = 4.869	0.027
No	3709 (85.21)	3164 (85.72)	545 (82.33)		
Yes	644 (14.79)	527 (14.28)	117 (17.67)		
Cancer, n (%)				$\chi2$ = 0.002	0.961
No	4311 (99.04)	3656 (99.05)	655 (98.94)		
Yes	42 (0.96)	35 (0.95)	7 (1.06)		
Chronic lung diseases, n (%)				$\chi2$ = 13.482	<0.001
No	4016 (92.26)	3429 (92.90)	587 (88.67)		
Yes	337 (7.74)	262 (7.10)	75 (11.33)		
Liver disease, n (%)				$\chi2$ = 4.887	0.027
No	4224 (97.04)	3591 (97.29)	633 (95.62)		
Yes	129 (2.96)	100 (2.71)	29 (4.38)		
CKD, n (%)				$\chi2$ = 6.205	0.013
No	4160 (95.57)	3540 (95.91)	620 (93.66)		
Yes	193 (4.43)	151 (4.09)	42 (6.34)		
Antihyperlipidemic drug, n (%)				$\chi2$ = 20.305	<0.001
No	4202 (96.53)	3583 (97.07)	619 (93.50)		
Yes	151 (3.47)	108 (2.93)	43 (6.50)		
CRP, mg/L, M (Q_1, Q_3)	0.94 (0.51, 1.91)	0.89 (0.50, 1.87)	1.22 (0.57, 2.15)	W = 1096581.500	<0.001

Table 1: (continued)

Variables	Total (N=4353)	Non-CVD/stroke (N=3691)	CVD/stroke (N=662)	Statistics	P
UA, mg/dL, M (Q_1, Q_3)	4.21 (3.51, 5.05)	4.21 (3.51, 5.03)	4.23 (3.52, 5.11)	W = 1202510.000	0.519
Smoking, n (%)				$\chi2$ = 6.964	0.031
Non-smoker	2760 (63.40)	2337 (63.32)	423 (63.90)		
Ex-smoker	284 (6.52)	227 (6.15)	57 (8.61)		
Smoker	1309 (30.07)	1127 (30.53)	182 (27.49)		
Drinking alcohol, n (%)				$\chi2$ = 4.236	0.120
Never drinking	2570 (59.04)	2164 (58.63)	406 (61.33)		
Current drinking	280 (6.43)	231 (6.26)	49 (7.40)		
Former drinking	1503 (34.53)	1296 (35.11)	207 (31.27)		
Physical activity, MET·min/week, n (%)				$\chi2$ = 0.533	0.466
<600	2796 (64.23)	2362 (63.99)	434 (65.56)		
≥600	1557 (35.77)	1329 (36.01)	228 (34.44)		
BMI, kg/m2, n (%)				$\chi2$ = 21.631	<0.001
<24	2362 (54.26)	2050 (55.54)	312 (47.13)		
≥24	1530 (35.15)	1245 (33.73)	285 (43.05)		
Unknown	461 (10.59)	396 (10.73)	65 (9.82)		
Cumulative sdLDL-C mg/dL, M (Q_1, Q_3)	99.40 (82.21, 119.59)	98.33 (81.38, 118.79)	104.97 (87.98, 123.84)	W = 1060518.000	<0.001
Cumulative sdLDL-C mg/dL levels, n (%)				$\chi2$ = 23.096	<0.001
≤82.2	1089 (25.02)	966 (26.17)	123 (18.58)		
(82.2, 99.4]	1088 (24.99)	931 (25.22)	157 (23.72)		
(99.4, 120]	1088 (24.99)	902 (24.44)	186 (28.10)		
>120	1088 (24.99)	892 (24.17)	196 (29.61)		
sdLDL-C change groups, n (%)				$\chi2$ = 20.744	<0.001
Persistent low	582 (13.37)	524 (14.20)	58 (8.76)		
Persistent middle	762 (17.51)	639 (17.31)	123 (18.58)		
Persistent high	618 (14.20)	504 (13.65)	114 (17.22)		
Descending	1170 (26.88)	1005 (27.23)	165 (24.92)		
Increasing	1221 (28.05)	1019 (27.61)	202 (30.51)		
sdLDL-C, n (%)				$\chi2$ = 25.073	<0.001
Class 1	1859 (42.71)	1629 (44.13)	230 (34.74)		
Class 2	1838 (42.22)	1537 (41.64)	301 (45.47)		
Class 3	656 (15.07)	525 (14.22)	131 (19.79)		

t': Satterthwaite *t* test; χ^2: Rao-Scott Chi-square test; W: Wilcoxon rank sum test.
CVD: cardiovascular diseases, SD: standard deviation, DM: diabetes mellitus, CKD: chronic kidney disease, CRP: C-reaction protein, M: median, Q_1:1st quartile, Q_3: 3rd quartile, UA: uric acid, BMI: body mass index, sdLDL-C: small dense low-density lipoprotein cholesterol.

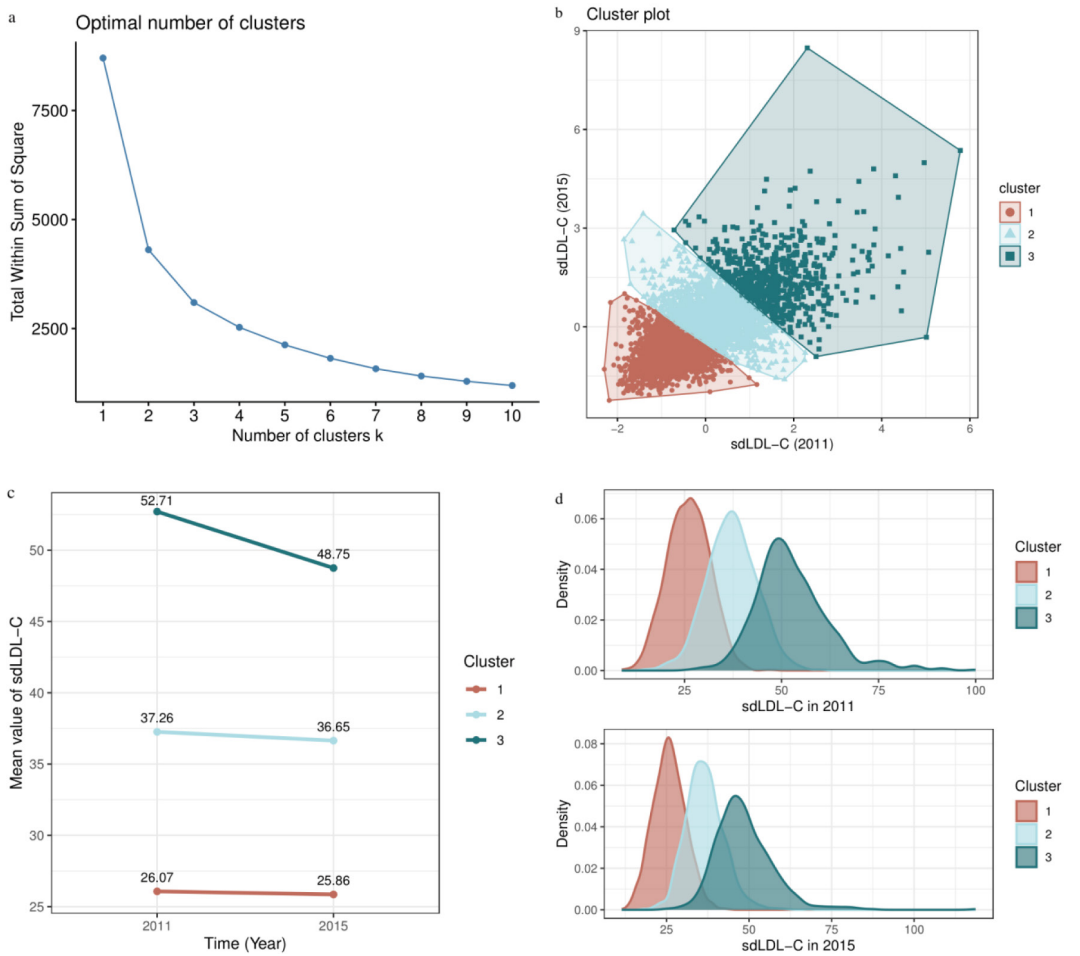

Figure 2. K-means Cluster analysis on sdLDL levels between 2011 and 2015. (a) line chart of sdLDL changes between 2011 and 2015. (b) individuals in three sdLDL classes and Euclidean distance of each cluster. (c) Data visualization for different classes of the change in the sdLDL. (d) Distribution of the sdLDL in three classes in 2011 and 2015, respectively.

between sdLDL-C and stroke (Figure 3c).

DISCUSSION

This study included middle-aged and old adults from the CHARLS database to evaluate the associations of cumulative sdLDL-C, sdLDL-C change and sdLDL-C cluster with new-onset CVD or stroke among Chinese populations. This study revealed significant associations of elevated cumulative sdLDL-C and high sdLDL-C change levels with an increased risk of new-onset CVD/stroke. Additionally, our results showed linear relationships of sdLDL-C with the risks of CVD/stroke and CVD.

These findings were aligned with previous evidence on the relationship between sdLDL-C and cardiovascular and cerebrovascular diseases risk. Zhang *et al*.[16] identified that a high level of estimated sdLDL-C is associated with increased risk of atherosclerotic cardiovascular disease based on the Korea National Health and Nutrition Examination Survey (KNHANES) database. Another study utilized prospective longitudinal data from a general Japanese population, suggesting that serum sdLDL-C level is a relevant biomarker for the future development of coronary heart disease that offers benefit beyond the serum LDL-C level.[17] Our study results showed that cumulated sdLDL-C and high sdLDL-C change levels were both associated with increased risk of CVD, which supplemented the information on potential role of dynamic change of sdLDL-C in further CVD/stroke risk. However, no significant relationship between cumulative sdLDL-C or sdLDL-C change and stroke risk was observed in current study. In fact, Duran *et al*.[18] have reported

Table 2: Associations of cumulative sdLDL-C and sdLDL-C change with CVD or stroke

Variables	Sample size (outcome/ total)	Unadjusted mode		Adjusted model*	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Cumulative sdLDL mg/dL					
≤82.2	123/1089	Ref		Ref	
(82.2, 99.4]	157/1088	1.32 (1.03-1.71)	0.029	1.23 (0.95-1.60)	0.110
(99.4, 120]	186/1088	1.62 (1.27-2.07)	<0.001	1.44 (1.12-1.86)	0.005
>120	196/1088	1.73 (1.36-2.20)	<0.001	1.41 (1.09-1.82)	0.010
sdLDL change					
Persistent low	58/582	Ref		Ref	
Persistent middle	123/762	1.74 (1.25-2.44)	0.001	1.56 (1.12-2.21)	0.010
Persistent high	114/618	2.04 (1.46-2.88)	<0.001	1.62 (1.14-2.32)	0.008
Descending	165/1170	1.48 (1.09-2.05)	0.015	1.37 (0.99-1.91)	0.058
Increasing	202/1221	1.79 (1.32-2.46)	<0.001	1.56 (1.14-2.17)	0.006
sdLDL cluster					
Class 1	230/1859	Ref		Ref	
Class 2	301/1838	1.39 (1.15-1.67)	0.001	1.25 (1.03-1.52)	0.022
Class 3	131/656	1.77 (1.39-2.23)	<0.001	1.46 (1.14-1.88)	0.003

sdLDL-C: small dense low-density lipoprotein cholesterol, CVD: cardiovascular disease, OR: odds ratio, CI: confidence intervals, Ref: reference.

*Adjusted for age, gender, hypertension, chronic lung diseases, liver disease, CKD, antihyperlipidemic drug, smoking and BMI.

that elevated levels of sdLDL-C serve as a more significant predictor of myocardial infarction (MI) but are not significantly associated with incident ischemic stroke (IS). Since a high level of cumulative sdLDL-C and increased sdLDL-C change levels were linked to increased odds of CVD/stroke, lipid screening in middle-aged and old adults, especially the dynamic change of sdLDL-C, supplemented by tailored exercise programs creation, health education and lifestyle promotion, may help prevent and reduce potential cardiovascular and cerebrovascular disease risk.

According to previous studies, sdLDL-C may be related to the instability of atherosclerotic plaques and their vulnerability to rupture. Thin fibrous caps and large lipid or necrotic cores are the main characteristics of unstable plaques in fibrous atheroma, which often trigger acute rupture and erosion, leading to subsequent vascular events. The plaques in coronary artery disease are thin-capped, and in atherosclerotic cerebrovascular disease, there is a mixture of thin-capped and thick-capped fibrous atheromatous plaques.[19] This evidence to some extent may explain the underlying mechanisms of relationship between sdLDL-C and CVD/stroke we observed. Besides, a study showed that while positive associations were identified between LDL-C and the development of large vessel atherosclerotic subtypes of IS, no significant associations exist between LDL-C and cardioembolic subtypes.[20] Whereas Zhou *et al*.[21] reported that sdLDL-C is an independent risk factor for IS, especially for non-cardioembolic stroke. A prospective study involved 38,319 individuals from the Copenhagen General Population Study who provided recent measurements of sdLDL-C levels and reported that higher levels of sdLDL-C were strongly linked to an increased risk of IS.[22] These differences may stem from strict criteria and varied study populations. In the present study, compared to persistent low levels of sdLDL-C from 2011 to 2015, an increase in sdLDL-C levels was slightly associated with stroke risk in the middle-aged and old adults, the OR value was greater than 1 and the P-value showed marginal significance. This indicated that further detailed subgroup analysis and prospective studies are needed to validate the relationships of cumulative sdLDL-C and sdLDL-C change with stroke risk.

The RCS curve indicated linear associations

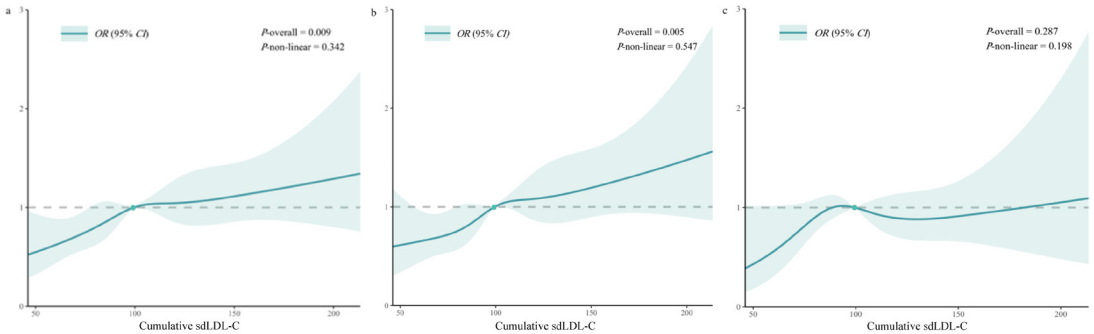

Figure 3. RCS of the cumulative sdLDL between 2011 and 2015 with CVD/stroke. (a) RCS for association between cumulative sdLDL and CVD/stroke. (b) RCS for association between cumulative sdLDL and CVD. (c) RCS for association between cumulative sdLDL and stroke.

of cumulative levels of sdLDL-C from 2011 to 2015 with the risk of CVD/stroke and CVD in middle-aged and old adults in China. Previous research has suggested that sdLDL-Cl showed a log-linear association with IS in a multivariate adjusted cubic spline model.[22] The strong association we observed between elevated cumulative sdLDL-C levels and increased risk of CVD underscored the potential for incorporating sdLDL-C measurements into routine CVD risk assessments. Additionally, given that current guidelines primarily emphasize total cholesterol and LDL-C levels, our findings advocate for a paradigm shift towards a more nuanced understanding of lipid profiles. This is particularly pertinent for patients with existing risk factors such as hypertension and DM, for whom cumulative sdLDL-C and its change could serve as critical biomarkers for early identification and intervention strategies aimed at reducing cardiovascular risks.

Our research offered valuable insights but still has some limitations. First, potential biases caused by the retrospective design of this study may influence explanation on analysis results. Second, various data extracted from the CHARLS database reliance on self-reported, leading to recalling bias. Third, insufficient follow-up duration made it hard to capture cumulative sdLDL-C levels in long-term periods as well as cardiovascular health. Lastly, the lack of laboratory experiments may restrict causal inferences and mechanisms exploration. Future studies should use longitudinal designs and experimental methods to validate relationships and the mechanisms linking sdLDL-C to cardiovascular and cerebrovascular diseases.

In conclusion, the results of this study indicated that both high levels of cumulative sdLDL and increases in sdLDL change over time are linked to an increased risk of CVD or stroke in middle-aged and old adults. It is recommended to focus on timely blood lipid health monitoring in this population, creating targeted improvement strategies according to the relevant guidelines, providing health education, and promoting healthier lifestyle changes to help prevent disease occurrence and reduce disease burden.

DISCLOSURE

Ethics: Due to the data from CHARLS databases were publicly available, ethical approval had been waived from the IRB of the Renmin Hospital, Hubei University of Medicine.

Data availability: The datasets generated during and/or analyzed during the current study are available in the CHARLS webpage: https://charls.charlsdata.com/pages/Data/2020-charls-wave5/zh-cn.html.

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Table S1: Variables with missing values

Variables	N (%)	Total samples
Hypertension	2 (0.05)	4351
Education level	4 (0.09)	4349
Drinking	4 (0.09)	4349
Chronic lung diseases	7 (0.16)	4346
Liver disease	15 (0.34)	4338
Cancer	16 (0.37)	4337
Smoking	54 (1.24)	4299
BMI	461 (10.59)	3892
Annual income	2884 (66.25)	1469

BMI: body mass index.

Table S2: Sensitivity analysis before and after interpolation of missing data

Variables	Total	Before interpolation	After interpolation	Statistics	*P*
Hypertension, n (%)				$\chi^2 = 0.000$	1.000
No	4463 (51.26)	2232 (51.27)	2231 (51.25)		
Yes	4241 (48.71)	2121 (48.73)	2120 (48.70)		
Education level, n (%)				$\chi^2 = 0.001$	0.999
No formal education	2370 (27.22)	1185 (27.22)	1185 (27.22)		
Primary school	3603 (41.39)	1803 (41.42)	1800 (41.35)		
Middle school or above	2729 (31.35)	1365 (31.36)	1364 (31.33)		
Drinking alcohol, n (%)				$\chi^2 = 0.000$	1.000
Never drinking	5137 (59.01)	2570 (59.04)	2567 (58.97)		
Current drinking	560 (6.43)	280 (6.43)	280 (6.43)		
Former drinking	3005 (34.52)	1503 (34.53)	1502 (34.50)		
Chronic lung diseases, n (%)				$\chi^2 = 0.000$	1.000
No	674 (7.74)	337 (7.74)	337 (7.74)		
Yes	8025 (92.18)	4016 (92.26)	4009 (92.10)		
Liver disease, n (%)				$\chi^2 = 0.000$	1.000
No	258 (2.96)	129 (2.96)	129 (2.96)		
Yes	8433 (96.86)	4224 (97.04)	4209 (96.69)		
Cancer, n (%)				$\chi^2 = 0.000$	1.000
No	84 (0.96)	42 (0.96)	42 (0.96)		
Yes	8606 (98.85)	4311 (99.04)	4295 (98.67)		
Smoking, n (%)				$\chi^2 = 0.108$	0.947
Non-smoker	5495 (63.12)	2759 (63.38)	2736 (62.85)		
Ex-smoker	567 (6.51)	284 (6.52)	283 (6.50)		
Smoker	2590 (29.75)	1310 (30.09)	1280 (29.41)		

χ^2: Chi-square test.

Table S3: Results of covariable selection using bidirectional stepwise regression

Variables	CVD or stroke		CVD only		Stroke only	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.001	1.03 (1.01-1.05)	0.001
Gender					-	
Male	Ref		Ref			
Female	1.34 (1.05-1.71)	0.018	1.45 (1.19-1.75)	<0.001		
Hypertension						
No	Ref		Ref		Ref	
Yes	1.53 (1.28-1.83)	<0.001	1.63 (1.33-1.99)	<0.001	1.35 (1.01-1.81)	0.046
Chronic lung diseases					-	
No	Ref		Ref			
Yes	1.54 (1.16-2.03)	0.002	1.62 (1.19-2.18)	0.002		
Liver disease					-	
No	Ref		Ref			
Yes	1.57 (1.00-2.40)	0.040	1.70 (1.05-2.66)	0.025		
CKD			-		-	
No	Ref				Ref	
Yes	1.50 (1.03-2.13)	0.030			2.30 (1.39-3.64)	0.001
Antihyperlipidemic drug						
No	Ref		Ref		Ref	
Yes	1.88 (1.28-2.71)	0.001	1.91 (1.27-2.82)	0.001	1.91 (1.06-3.23)	0.022
Smoking			-			
Non-smoker	Ref				Ref	
Ex-smoker	1.50 (1.04-2.15)	0.028			2.62 (1.71-3.92)	<0.001
Smoker	1.10 (0.85-1.43)	0.458			1.23 (0.90-1.68)	0.184
BMI						
<24	Ref		Ref		Ref	
≥24	1.43 (1.19-1.72)	<0.001	1.43 (1.17-1.76)	0.001	1.47 (1.08-1.99)	0.013
Unknown	1.26 (0.93-1.69)	0.120	1.44 (1.04-1.97)	0.025	1.06 (0.62-1.73)	0.815

CVD: cardiovascular disease, OR: odds ratio, CI: confidence interval, Ref: reference, CKD: chronic kidney disease, BMI: body mass index.

AIC of CVD or stroke model = 3619.19; AIC of CVD model = 3111.07; AIC of stroke model = 1705.27.

Table S4: Associations between sdLDL-C and CVD

Variables	Sample size (outcome/ total)	Unadjusted model		Adjusted model*	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Cumulative sdLDL mg/dL					
≤82.2	96/1089	Ref		Ref	
(82.2, 99.4]	113/1088	1.20 (0.90-1.60)	0.214	1.08 (0.81-1.45)	0.595
(99.4, 120]	148/1088	1.63 (1.24-2.14)	<0.001	1.40 (1.06-1.86)	0.018
>120	166/1088	1.86 (1.43-2.44)	<0.001	1.45 (1.09-1.92)	0.011
sdLDL change					
Persistent low	43/582	Ref		Ref	
Persistent middle	93/762	1.74 (1.20-2.57)	0.004	1.48 (1.01-2.20)	0.045
Persistent high	97/618	2.33 (1.61-3.44)	<0.001	1.73 (1.17-2.58)	0.007
Descending	133/1170	1.61 (1.13-2.33)	0.010	1.40 (0.98-2.05)	0.071
Increasing	157/1221	1.85 (1.31-2.66)	0.001	1.54 (1.08-2.24)	0.018
sdLDL cluster					
Class 1	171/1859	Ref		Ref	
Class 2	240/1838	1.48 (1.21-1.83)	<0.001	1.31 (1.06-1.62)	0.014
Class 3	112/656	2.03 (1.57-2.62)	<0.001	1.63 (1.24-2.14)	<0.001

sdLDL-C: small dense low-density lipoprotein cholesterol, CVD: cardiovascular disease, OR: odds ratio, CI: confidence intervals, Ref: reference.

*Adjusted for age, gender, hypertension, chronic lung diseases, liver disease, antihyperlipidemic drug and BMI.

Table S5: The associations of sdLDL with Stroke only

Variables	Sample size (outcome/ total)	Unadjusted model		Adjusted model*	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Cumulative sdLDL mg/dL					
≤82.2	41/1089	Ref		Ref	
(82.2, 99.4]	64/1088	1.60 (1.07-2.40)	0.022	1.56 (1.04-2.37)	0.032
(99.4, 120]	59/1088	1.47 (0.98-2.22)	0.066	1.37 (0.91-2.10)	0.138
>120	58/1088	1.44 (0.96-2.18)	0.081	1.26 (0.82-1.95)	0.289
sdLDL change					
Persistent low	21/582	Ref		Ref	
Persistent middle	42/762	1.56 (0.92-2.71)	0.104	1.54 (0.91-2.71)	0.118
Persistent high	36/618	1.65 (0.96-2.91)	0.074	1.47 (0.84-2.64)	0.188
Descending	48/1170	1.14 (0.69-1.97)	0.617	1.17 (0.70-2.04)	0.556
Increasing	75/1221	1.75 (1.09-2.93)	0.027	1.66 (1.02-2.82)	0.049
sdLDL cluster					
Class 1	88/1859	Ref		Ref	
Class 2	91/1838	1.05 (0.78-1.42)	0.758	0.97 (0.71-1.33)	0.866
Class 3	43/656	1.41 (0.96-2.04)	0.072	1.22 (0.81-1.80)	0.332

sdLDL-C: small dense low-density lipoprotein cholesterol, CVD: cardiovascular disease, OR: odds ratio, CI: confidence intervals, Ref: reference.

*Adjusted for age, hypertension, CKD, antihyperlipidemic drug, smoking and BMI.