Lipids in Health and Disease

RESEARCH Open Access

An equation for calculating small dense low-density lipoprotein cholesterol

Tianjiao Han[1†], Zhe Piao[1†], Zhiguo Yu[2†], Wanqi Xu[1] and Xiaofeng Cui[1*]

Abstract

Objective Small dense low-density lipoprotein cholesterol (sdLDL-C), as an emerging atherogenic factor of cardiovascular diseases, requires additional tests. We aimed to establish a sdLDL-C equation using standard lipid profile and evaluate its capacity of identifying the residual cardiovascular risk beyond LDL-C and apolipoprotein B (ApoB).

Methods This cross-sectional study included 25 435 participants from Health Management Cohort and 11 628 participants from China Health and Retirement Longitudinal Study (CHARLS) to construct and evaluate the sdLDL-C equation by least-squares regression model. The equation for sdLDL-C depended on low-density lipoprotein cholesterol (LDL-C) and an interaction term between LDL-C and the natural log of triglycerides (TG).

Results The modified equation (sdLDL-C = 0.14*ln(TG)*LDL-C − 0.45*LDL-C + 10.88) was more accurate than the original equation in validation set (slope = 0.783 vs. 0.776, MAD = 5.228 vs. 5.396). Using the 80th percentile (50 mg/dL) as a risk-enhancer rule for sdLDL-C, accuracy of the modified equation was higher than the original equation in validation set (90.47% vs. 89.73%). The estimated sdLDL-C identified an additional proportion of high-risk individuals in BHMC (4.93%) and CHARLS (1.84%).

Conclusion The newly developed equation in our study provided an accurate tool for estimating sdLDL-C level among the Chinese population as a potential cardiovascular risk-enhancer.

Keywords small dense low-density lipoprotein cholesterol (sdLDL-C), LDL cholesterol, apolipoprotein B (ApoB), cardiovascular disease

Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide [1] and the estimated prevalence of ASCVD reached 32.2% among Chinese population in 2022 [2]. Moreover, ASCVD caused 40% deaths in China [3] and imposed a substantial burden on human health. The increasing level of low-density lipoprotein cholesterol (LDL-C) is strongly associated with the development and progression of ASCVD, becoming the principal target for the primary and secondary prevention [4, 5]. Unfortunately, recent studies pointed out that residual ASCVD risk remained even in people achieving appropriate LDL-C level [6, 7]. LDL

†First authors: Tianjiao Han, Zhe Piao, and Zhiguo Yu analyzed the data and drafted the manuscript together.

*Correspondence:
Xiaofeng Cui
xfcui@jlu.edu.cn
[1]China-Japan Union Hospital of Jilin University, Jilin University, Changchun, China
[2]First Affiliated Hospital of Kunming Medical University, Yunnan, China

subfractions can be classified based on density and size. In general, there are two major LDL sizes, that are small and dense LDL (sdLDL) characterized by high density and large buoyant LDL (lbLDL). Thus, not only the amount of LDL-C, but the composition should be considered for the risk stratification of ASCVD. The cholesterol component on sdLDL particles (sdLDL-C) has been recognized as an emerging atherogenic risk factor accounting for residual risk of ASCVD by National Cholesterol Education Program [8]. Shiffman et al., revealed that sdLDL-C is independently associated with ASCVD [9] independent of traditional lipid parameters. In addition, previous studies found that sdLDL-C could predict the development of acute ischemic stroke [10] and coronary heart disease [11], even among participants with recommended LDL-C level (12–13). A study from Framingham Offspring Cohort confirmed the improved capacity of integrating sdLDL-C into the risk stratification and management of ASCVD [14]. Therefore, it is of great importance to facilitate the routine detection of sdLDL-C.

Ultracentrifugation or gradient gel electrophoresis are used as traditional measurements of sdLDL-C [15] with restricted usability in the large-scale population studies or screening programs due to the intensive labor, time and cost. Two equations have been proposed to estimate sdLDL-C level. Burns et al., developed a sdLDL-C equation using the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C) and nonHDL-C concentration only in 141 youth [16]. Srisawasdi et al., constructed an equation among 297 adults with a restricted applicability [17]. A recent study [18] proposed a simple equation using TG and calculated LDL-C by Sampson equation. The compositions of LDL particles vary in different populations [19]; however, this novel equation has not been validated in the Chinese population.

Therefore, we aimed to develop and validate a modified equation of sdLDL-C using directly measured LDL-C level among the Chinese population, compare the modified equation with Sampsons sdLDL-C equation, and investigate the capacity of estimated sdLDL-C as an ASCVD risk-enhancer in two large populations.

Materials and methods

Data sources and study population

Two datasets were used in our study. The Health Management Cohort (HMC) is a large and dynamic cohort study, aiming to investigate the risk factors and biomarkers of cardio-metabolic disorders [20]. There were 25,435 participants with available lipid data enrolled in this current study from HMC between 2019 and 2021, and then randomly divided into training set (n=12717) and validation set (n=12718). The modified equation for calculating sdLDL-C was developed using HMC datasets. The capacity of estimated sdLDL-C as an ASCVD risk-enhancer was assessed in HMC and China Health and Retirement Longitudinal Study (CHARLS). CHARLS is a national cohort study initiated from 2011 among Chinese people aged 45 years or older [21]. A total of 11,628 participants of CHARLS at baseline with available lipid data were enrolled in the final analysis.

Ethics statement

This study was in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Peking University (IRB00001052-11015). All participants have provided written informed consents. This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Lipid measurement

Concentrations of TG was directly measured using the enzymatic colorimetric method (GPO/PAP) and surfactant assay method based on the automatic biochemical analyzer BECKMAN COULTER AU5800. Total cholesterol and HDL-C levels were directly measured by enzymatic method (Pureauto S CHO-N) and catalase assay. Apolipoprotein B (ApoB) was directly measured by immunoturbidimetry method in BHMC. The measurements of TG, HDL-C and TC in CHARLS was previously described [21]. Given that the direct measurement methods of LDL-C are influenced by the content of cholesterol and triglycerides, particularly in hypertriglyceridemia, LDL-C was calculated by the Sampson equations [22–24]. The nonHDL-C was calculated as total cholesterol minus HDL-C. The sdLDL-C=0.14* Ln(TG)* LDL-C −0.43* LDL-C+8.99 according Sampson sdLDL-C equation as the original equation.

The sdLDL-C concentration was directly measured among BHMC participants by the sdLDL-C test kit (Denka) using catalase method with an intra-assay coefficient of variation (CV)<6.0% and a correlation efficient (r)≥0.975. The sdLDL-C test process was a fully automatic two-step assay. Step 1: lipoprotein particles except for LDL in serum samples were degraded by specific surfactants. Then, two subgroups of LDL, that are lbLDL and intermediate density LDL (idLDL) were degraded by tool enzymes. Apart from sdLDL-C, the cholesterol of lbLDL and idLDL were decomposed by cholesterol esterase and cholesterol oxidase, and the generated H_2O_2 was removed by catalase. Step 2: The chemical composition of the reaction solution was changed to inhibit the activity of catalase. The remaining sdLDL in the sample was degraded and the cholesterol component was then released. The H_2O_2 generated during the enzymatic decomposition of sdLDL-C in the tinder reaction, thereby completing the quantitative detection of

sdLDL-C. The lb-LDL-C was calculated by subtracting measured sdLDL-C from estimated LDL-C by Sampson equation.

Covariates

The demographic characteristics, smoking status, physical activity and history of diseases (hypertension and diabetes) were collected via a standard questionnaire. Anthropometric measurements were performed for height and body weight. Body mass index (BMI) was calculated as weight (in kilograms)/height squared (in meters squared). Systolic blood pressure was presented as the average of two measurements on the right arm using a sphygmomanometer after resting for at least 10 min.

Table 1 Characteristics of participants

	Overall population
Participants, No.	25,435
Sex, No. (%)	
Female	12,311 (48.4)
Male	13,124 (51.6)
Age, years	
Mean (SD)	44 (13)
Median (IQR)	42 [34, 53]
Min - Max	18–96
Triglycerides, mg/dL	
Median (IQR)	97.46 [66.45, 145.30]
Min - Max	26.58–2245.12
Total cholesterol, mg/dL	
Median (IQR)	191.75 [168.56, 217.27]
Min - Max	71.13–532.73
LDL cholesterol, mg/dL	
Median (IQR)	119.32 [98.13, 142.18]
Min - Max	7.54–459.27
Measured sd-LDL cholesterol, mg/dL	
Median (IQR)	35.18 [25.52, 47.17]
Min - Max	8.12–123.71
NonHDL cholesterol, mg/dL	
Median (IQR)	140.72 [116.37, 166.62]
Min - Max	24.36–497.94
HDL cholesterol, mg/dL	
Median (IQR)	49.48 [41.75, 58.38]
Min - Max	16.24–128.35
ApoB, mg/dL	
Median (IQR)	45.50 [38.00, 53.00]
Min - Max	12.50–110.00

Data are presented as mean (SD), median [IQR], min-max or number (%), as appropriate

Abbreviation: BHMC: Beijing Health Management Cohort; SD, standard derivation; IQR, interquartile range; LDL, low-density lipoprotein; sdLDL, small-dense low-density lipoprotein; HDL, high-density lipoprotein; ApoB, apolipoprotein B

To convert triglycerides from mg/dL to mmol/L, divided by 88.6; to convert cholesterol from mg/dL to mmol/L, divided by 38.66; ApoB from mg/dL to μmol/L, multiply by 0.02

Statistical analysis

An equation for estimating sdLDL-C was developed by partial least-square regression analysis. The estimated sdLDL-C depended on the estimated LDL-C and an interaction term between LDL-C and the natural log of TG based on the training set of BHMC. The residual errors, slope, coefficient of determination (R [2]), mean absolute deviation (MAD) and root mean square error (RMSE) between the measured and estimated sdLDL-C were calculated to assess the equation accuracy both among the training and validation datasets. The accuracy of sdLDL-C equation was evaluated stratified by TG and LDL-C intervals. In addition, we used the 80th percentile (50 mg/dL) as cutoff value of high sdLDL-C. We calculated the classification accuracy, false negative rate and false positive rate correspondingly. Furthermore, we compared the performance of the modified sdLDL-C equation in our study with a previous sdLDL-C estimation tool based on the calculated LDL-C. Given the potential impact of lipid-lowering medication on sdLDL-C concentration, we re-assessed the accuracy of the sdLDL-C equation among people using lipid-lowering medication.

Population characteristics were shown as median (interquartile ranges), mean (standard deviation), or number (percentage). The differences of the characteristics were compared by Student's t-test or Mann-Whitney U test for continuous variables and Chi-square test for categorical variables according to training and validation datasets. In addition, we evaluated the capacity of estimated sdLDL-C (>50 mg/dL) as an extra risk-enhancer rule using BHMC and CHARLS datasets. Traditional ASCVD risk rules were set as TG>175 mg/dL or LDL-C>160 mg/dL or nonHDL-C>190 mg/dL by the 2018 Multi-society guideline of lipid management [25]. All statistical analyses were performed using R software (version 4.1.3). Two-sided P value<0.05 was considered statistically significant.

Results

Population characteristics

A total of 25,435 participants were enrolled from BHMC. The characteristics of BHMC population were shown in Table 1. The mean age was 44 years (ranging from 18 to 96 years), and 13,124 (51.6%) were male. The median (interquartile range, IQR) of TG, estimated LDL-C and sdLDL-C were 97.46 (66.45, 145.30) mg/dL, 119.32 (98.13, 142.18) mg/dL and 35.18 (25.52, 47.17) mg/dL, respectively. Table S1 compared the characteristics of participants between training and validation set, and no significant differences were observed for sex, age, TG, total cholesterol, LDL-C, sdLDL-C, HDL-C and nonHDL-C. We used the lipid profile data of 11,628 participants from CHARLS. The mean age was 59 years

(ranging from 22 to 99 years), including 5399 (46.5) males as shown in Table S2.

Relationship of sdLDL-C with TG and LDL-C

The proportions of lbLDL-C and sdLDL-C along with TG and LDL-C intervals were shown in Figure S1. In general, the proportion of sdLDL-C gradually increased with higher TG levels, but dependent of LDL-C intervals. Figure S2 presents the correlation of measured sdLDL-C with LDL-C and TG. The measured sdLDL-C concentration was positively correlated with LDL-C, in which TG amplified this association (Figure S2, **A**). The higher percentiles of TG increased the slope of sdLDL-C concentration with LDL-C. Similarly, we detected an approximate linear relationship between measured sdLDL-C concentration and the natural log of TG (Figure S2, **B**).

Evaluation of sdLDL-C equation

The modified equation for estimating sdLDL-C was as follows:

$$sdLDL\text{-}C = 0.14^{*}\ln(TG)^{*}LDL\text{-}C - 0.45^{*}LDL\text{-}C + 10.88.$$

Among the validation set, the slope between estimated and directly measured sdLDL-C was 0.783, the R^2 was 0.786, and the MAD was 5.228 for our modified equation (Fig. 1, A), which performed better than the original equation (Fig. 1, B). Individual points are colored according to the TG intervals, and the residual error indicated no systematic bias between estimated and directly measured sdLDL-C (Fig. 1, C-H). For the training set, the MAD was 5.327 and 5.498 for our modified and original equations as shown in Figure S3. Figure 2 presents the deviation of the modified and original sdLDL-C equations according to TG and LDL-C levels among the validation set. There demonstrated an overall higher accuracy of our modified equation than the original equation. The MAD and RMSE increased with high levels of TG (Fig. 2, A-B) and LDL-C (Fig. 2, C-D), especially when TG > 600 mg/dL. Results were consistent in the training set (Figure S4).

Using the 80th percentile (50 mg/dL) as cutoff value of high sdLDL-C level, we calculated the classification accuracy, false negative rate and false positive rate of the modified and original equations according to TG and LDL-C levels in the validation set (Fig. 3). Overall, the accuracy of sdLDL-C equations decreased with increased TG or LDL-C levels, and the modified equation had a better accuracy than original equation in regardless of TG and LDL-C intervals. Of note, the false negative rates were lower, and the false positive rates were higher for our modified equation compared with the original equation. The results on the validation set and exact numbers according to TG and LDL-C intervals are given in Table S3 to Table S6 Among 701 participants using lipid-lowering medication, the modified equation was more accurate than the original equation (accuracy: 94.86% vs. 94.44%) as shown in Figure S5. Our modified equation had a lower false negative rate (31.6% vs. 35.0%), and higher false positive rate (2.65% vs. 1.25%) compared with the original equation.

Estimated sdLDL-C as an additional cardiovascular risk-enhancer

We evaluated the capacity of estimated sdLDL-C as a novel ASCVD risk-enhancer using the 80th percentile (50 mg/dL) as cutoff value of high sdLDL-C based on BHMC and CHARLS datasets. In BHMC, the estimated sdLDL-C identified the greatest number of high-risk individuals (20.36%), followed by TG (16.64%), LDL-C (12.09%), and nonHDL-C (10.75%). In CHARLS, TG identified the largest number of high-risk individuals (19.64%), followed by estimated sdLDL-C (17.03%), LDL-C (10.61%), and nonHDL-C (10.41%) and of note, the estimated sdLDL-C independently recognized 1255 (4.93%) and 214 (1.84%) individuals of high ASCVD risk in BHMC and CHARLS.

Discussion

The main findings of our study are as follows: (1) we developed a modified equation for calculating sdLDL-C level using the directly measured LDL-C and TG concentrations without extra cost; (2) the modified equation improved the accuracy for calculating sdLDL-C among the Chinese population, especially reducing the false negative rate; and (3) the estimated sdLDL-C could be a novel risk-enhancer for ASCVD stratification and management.

There exist linear relationships of sdLDL-C with LDL-C and the natural log of TG as indicated in our study. And the proportion of sdLDL-C against lbLDL-C increases along with higher TG intervals. A previous study established an equation for calculating sdLDL-C using the calculated LDL-C [18]. Given the situation that LDL-C concentrations are directly measured by the automatic biochemical analyzer in current standard lipid profile, we developed a modified equation for sdLDL-C using directly measured LDL-C and TG concentrations among the Chinese population. Compared with the original equation, the new equation had a lower error and better accuracy for calculating sdLDL-C both on the training and validation sets. Of note, the modified equation lowered the false negative rate, although with a higher false positive rate. As a sdLDL-C calculation tool, the improved false negative rate is more important for the ASCVD risk stratification and screening application. For the first time, the newly developed equation provided a validated tool for sdLDL-C calculating for the Chinese population. The modified sdLDL-C equation enabled the application of sdLDL-C as potential markers

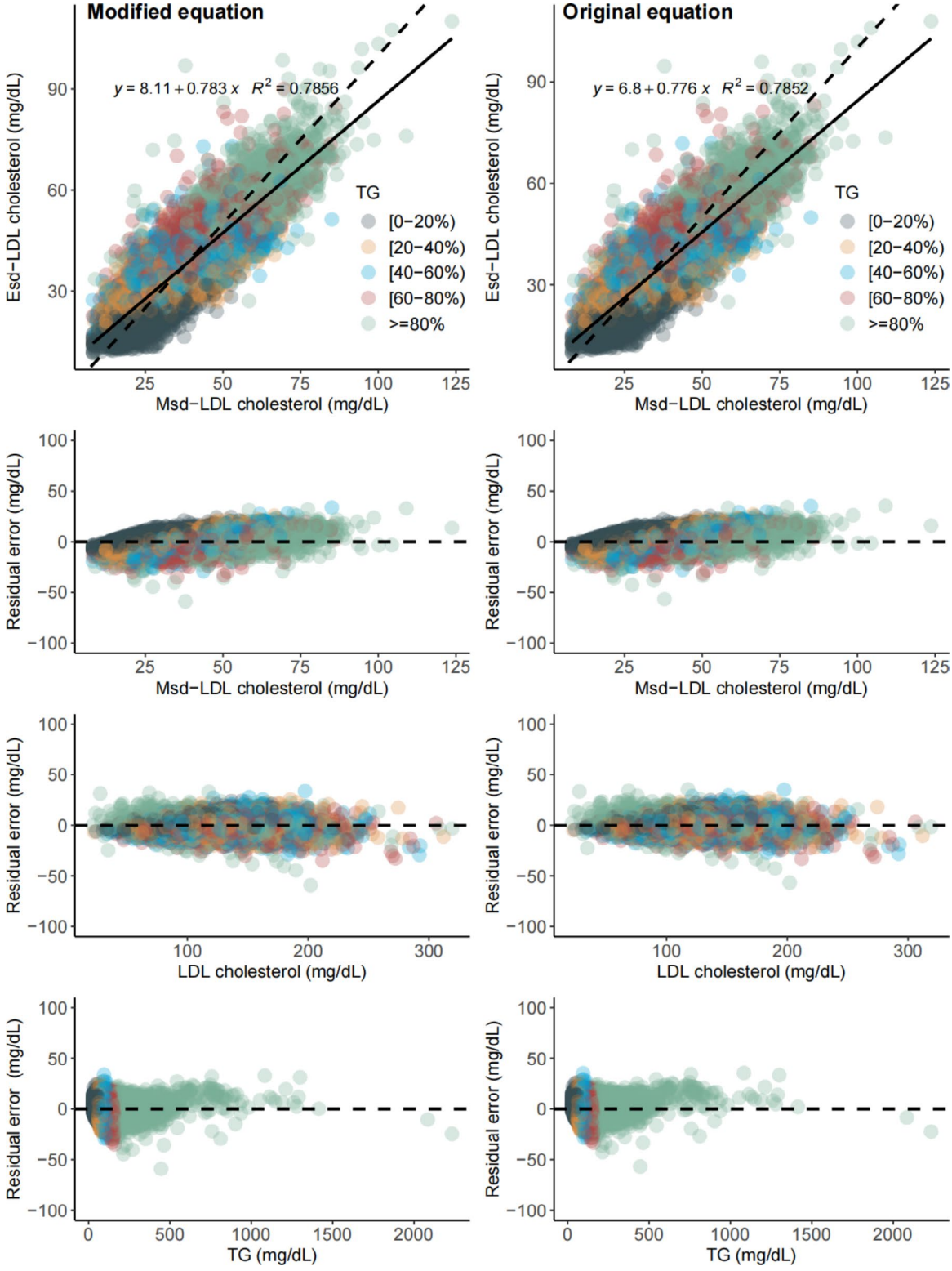

Fig. 1 Linear regression between estimated and measured small-dense low-density lipoprotein (sd-LDL) cholesterol levels in the validation set. Linear regression formulas using modified equation (**A**) and original equation (**B**). Solid line is the linear fitting for the indicated equation. Dotted line is the line of identity. Listed coefficient of determination (R [2]) and mean absolute deviation (MAD) are from the validation set, and the number in parentheses are from training set. Residual errors are plotted for measured sd-LDL (msd-LDL) cholesterol, LDL cholesterol, and triglycerides (TG) for modified equation (**C**, **E**, **G**) and original equation (**D**, **F**, **H**). Points are colored according to the TG intervals. Data of 12,718 participants in the validation set from Beijing Health Management Cohort were analyzed

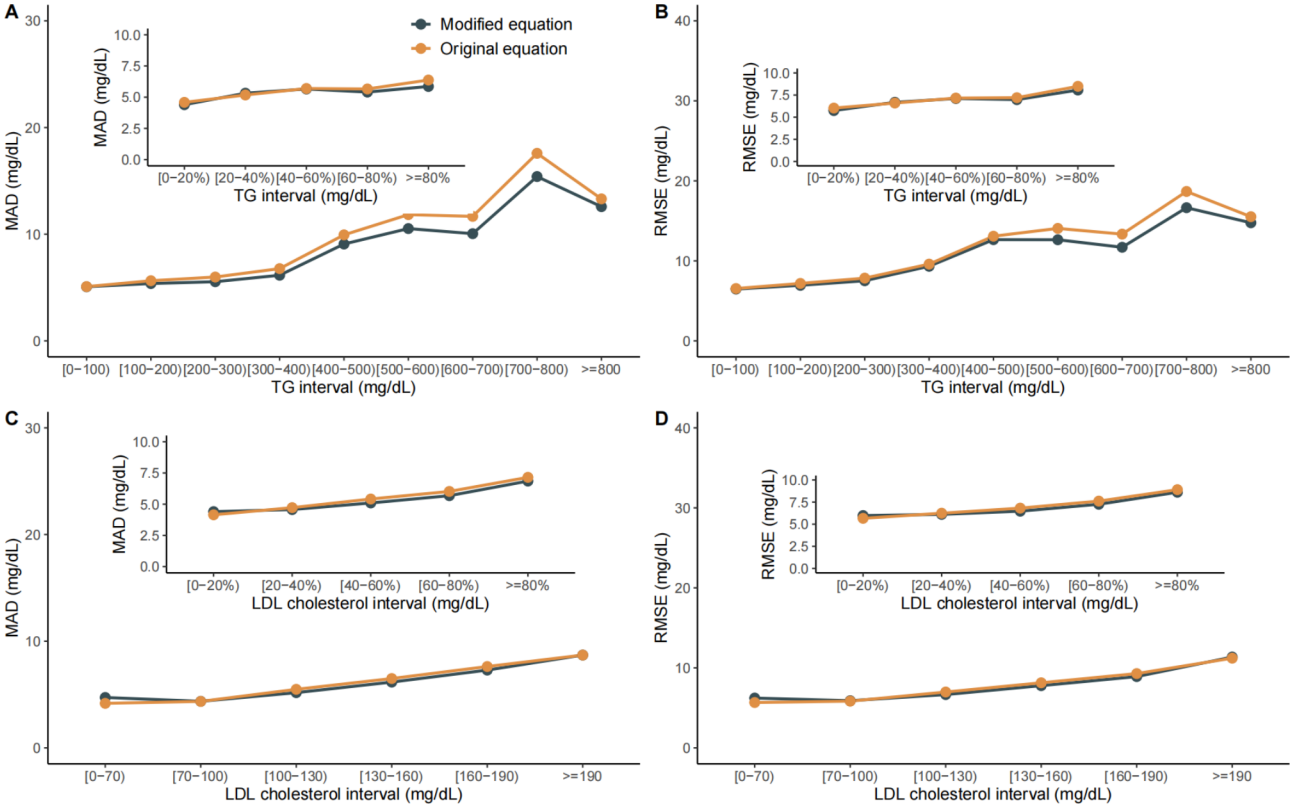

Fig. 2 Accuracy of modified and original equations for calculating small-dense low-density lipoprotein (sdLDL) cholesterol in the validation set. Mean absolute deviation (MAD) according to triglycerides (TG) intervals (**A**). Root mean square error (RMSE) according to TG intervals (**B**). MAD according to low-density lipoprotein (LDL) cholesterol intervals (**C**). RMSE according to LDL cholesterol intervals (**D**). Data of 12,718 participants in the validation set from Beijing Health Management Cohort were analyzed. Note: We compare the modified equation developed in this study with Sampsons sdLDL-C equation as the original equation

of cardio-metabolic disorders, which warranted further population-based studies and real-world evidence using standard lipid test without extra cost.

Furthermore, our study indicated that the estimated sdLDL-C could be a potential ASCVD risk-enhancer. The component proportions of LDL-C should be another focus of risk prediction or therapeutic strategies. In addition to the traditional risk rules (TG>175 mg/dL, LDL-C>160 mg/dL, nonHDL-C>190 mg/dL), high estimated sdLDL-C (>50 mg/dL) was set as a new risk-enhancer. We observed that the estimated sdLDL-C individually identified an additional 4.93% high-risk individuals in BHMC and 1.84% individuals in CHARLS. Of note, the LDL-C only recognized 2.58% additional individuals apart from TG, nonHDL-C and the estimated sdLDL-C in BHMC. The results indicated that sdLDL-C is probably the most atherogenic component of LDL-C. The estimated sdLDL-C could improve the risk stratification and management of ASCVD, which needs further validation.

Currently, the increasing popularity of LDL-C targeted therapy greatly contributes to the prevention of ASCVD [26]. However, a priori study revealed that the residual cardiovascular risk persisted, even after LDL-C controlled to a recommended level [6], becoming a clinical problem with growing importance. Some novel lipid parameters, such as triglycerides rich lipoprotein (TRL) and sdLDL-C, may explain the uncovered residual ASCVD risk [27]. A randomized controlled trial reported that sdLDL-C was strongly associated with myocardial infarction (MI) [28]. Mayu et al., found that sdLDL-C was a relevant biomarker for the development of coronary heart diseases [29]. A study indicated that sdLDL-C was significantly associated with the progression of any pre-existing coronary stenosis (RP) of non-culprit lesions in acute coronary syndrome patients [30]. Ikezaki et al., confirmed that sdLDL-C was the most atherogenic lipoprotein cholesterol parameter [14]. In statin-treated coronary artery diseases patients, sdLDL-C was associated with the recurrence of ASCVD independent of LDL-C [31]. In summary, the sdLDL-C level is of great importance for the ASCVD risk prevention and management. The fact is that the direct measurement of sdLDL-C concentration is not included in the standard lipid test in clinical and health examination practice due to the cost restriction and non-updated biochemical analyzer.

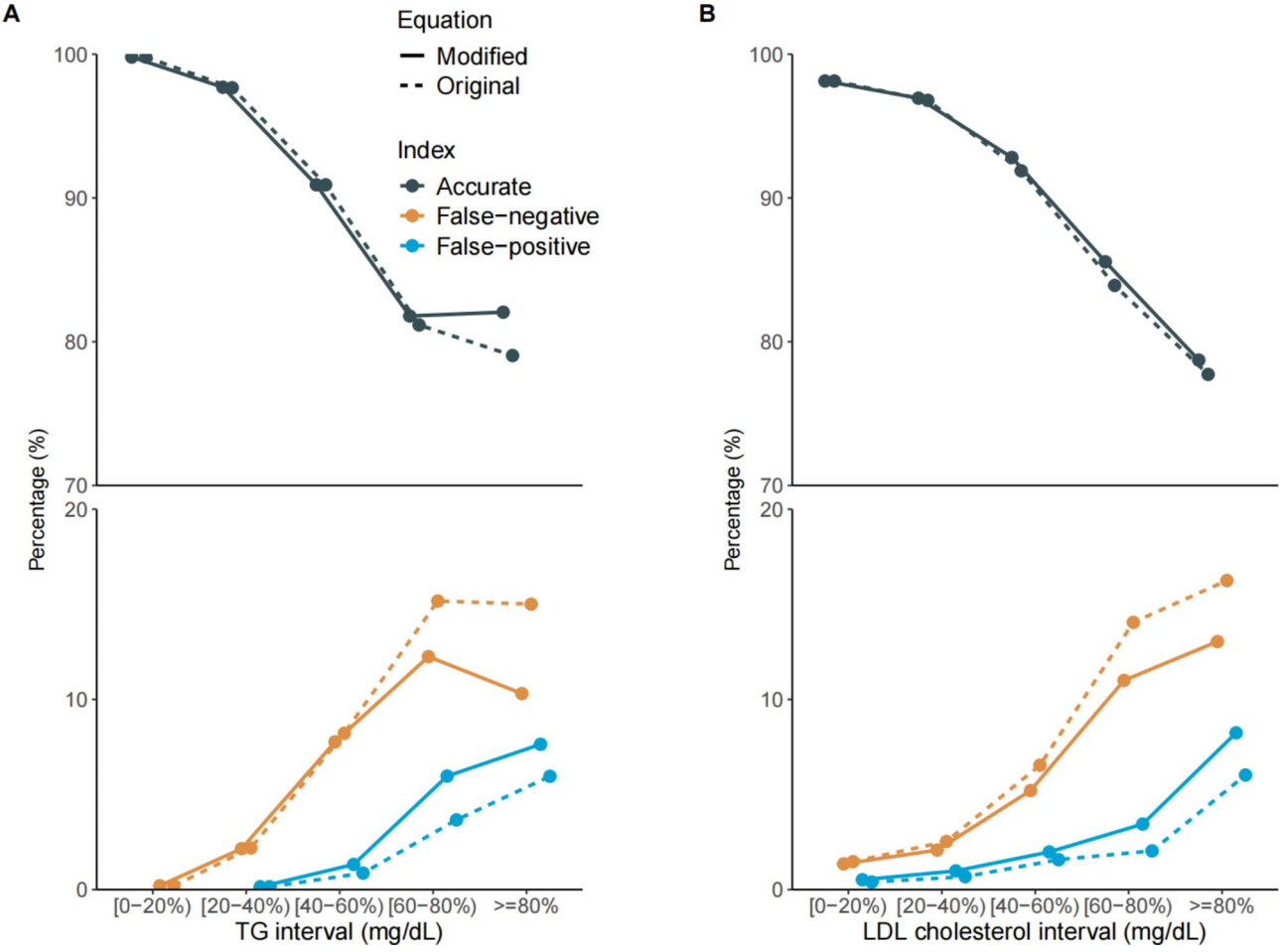

Fig. 3 Classification accuracy of modified and original equations for calculating small-dense low-density lipoprotein (sd-LDL) cholesterol in the validation set. The 80th percentile (50 mg/dL) of sd-LDL cholesterol as threshold. Accuracy and misclassification rates according to triglycerides (TG) intervals (**A**). Accuracy and misclassification rates according to LDL cholesterol intervals (**B**). Data of 12,718 participants in the validation set from Beijing Health Management Cohort were analyzed. Note: We compare the modified equation developed in this study with Sampsons sdLDL-C equation as the original equation

In this case, our study provided a simple and practical tool to calculate the sdLDL-C level. Using this sdLDL-C equation, the clinical value of sdLDL-C could be further explored in other metabolic diseases, while not limited to ASCVD.

Some studies further revealed the predictive ability of sdLDL-C. In liver transplant recipients, sdLDL-C independently predicted ASCVD events rather than LDL-C [32]. Li et al., found that sdLDL-C was associated with a higher risk of arterial stiffness [33]. A study in the urban Japanese population showed that sdLDL-C was a significant biomarker for predicting ASCVD [33]. As shown in our study, the estimated sdLDL-C could identify a larger proportion of individuals with high ASCVD risk than LDL-C and non-HDL-C. Recently, some large-scale risk assessment models including China-PAR Project were established to predict ASCVD risk [34–36]. However, sdLDL-C has not been integrated in the risk prediction model of ASCVD due to the cost of sdLDL-C test. The clinical guideline in China has not consider the residual risk-enhancers such as sdLDL-C [3]. The newly developed equation could provide an accurate estimation of sdLDL-C without extra cost, which has the clinical potential to improve the predictive capacity of current ASCVD risk assessment models among Chinese population.

There are several possible mechanisms that may explain the atherogenic effect of sdLDL. The sdLDL has a higher ability to penetrate vascular endothelium due to the small size [37], and has lower affinity for the LDL receptor. Thus, it tends to circulate in the bloodstream for a longer period [38]. In addition, sdLDL decreases receptor-mediated uptake, increases proteoglycan binding and oxidation susceptibility [30]. Through the above mechanisms, sdLDL-C could cause vascular damage, increase endometrial thickness, and further promote atherosclerosis [39]. There

is an urgent need to develop sdLDL-C targeted therapy beyond LDL-C lowering medication.

Limitations

Several limitations should be acknowledged in this current study. First, the accuracy of the developed sdLDL-C equation decreased among individuals with high TG or LDL-C levels. The equation needs further optimization, possibly by establishing targeted equations according to TG and LDL-C concentrations. The generalization of the newly developed equation needs further validation in other populations. Second, this is a cross-sectional study, and we were unable to investigate the effect of estimated sdLDL-C on the occurrence or recurrence of ASCVD. Our study indicated that the estimated sdLDL-C could be an independent risk-enhancer of ASCVD in the general population, which needs validation in further cohort studies.

In summary, our study developed an equation for estimating sdLDL-C among the Chinese population. The estimated sdLDL-C appeared to be a risk-enhancer of ASCVD beyond the standard lipid profiles, needing further research to evaluate the effect of calculated sdLDL-C on incidence of ASCVD.

Abbreviations

LDL-C	Low-density lipoprotein cholesterol
sdLDL-C	Small dense low-density lipoprotein cholesterol
lbLDL	large buoyant LDL
idLDL	intermediate density LDL
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
R^2	coefficient of determination
MAD	mean absolute deviation
RMSE	root mean square error
ASCVD	Atherosclerotic cardiovascular disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02345-0.

Supplementary Material 1

Supplementary Material 2

Author contributions

Xiaofeng Cui had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Tianjiao Han; Acquisition, analysis, or interpretation of the data: Zhe Piao, and Zhiguo Yu; Drafting of the manuscript: Tianjiao Han, and Wanqi Xu; Critical revision of the manuscript for important intellectual content: Xiaofeng Cui. The authors read and approved the final manuscript.

Funding

None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval statement.

This study was approved by the Institutional Review Board of Peking University (IRB00001052-11015). All participants have provided written informed consents.

Declaration of Sources of Funding

None.

Declaration of Conflicts of Interest

None.

Received: 26 July 2024 / Accepted: 23 October 2024
Published online: 08 November 2024

References

1. Lee MT, Mahtta D, Ramsey DJ, Liu J, Misra A, Nasir K, Samad Z, Itchhaporia D, Khan SU, Schofield RS, et al. <ArticleTitle Language="En">Sex-Related disparities in Cardiovascular Health Care among patients with premature atherosclerotic Cardiovascular Disease. JAMA Cardiol. 2021;6:782–90. https://doi.org/10.1001/jamacardio.2021.0683.
2. Hong T, Yan Z, Li L, Tang W, Qi L, Ye J, Ren J, Wan Q, Xiao W, Zhao D. The Prevalence of Cardiovascular Disease in Adults with Type 2 Diabetes in China: Results from the Cross-Sectional CAPTURE Study. Diabetes Therapy. 2022;13:969–81. https://doi.org/10.1007/s13300-022-01243-x.
3. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. Nat Reviews Cardiol. 2019;16:203–12. https://doi.org/10.1038/s41569-018-0119-4.
4. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–72. https://doi.org/10.1093/eurheartj/ehx144.
5. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC, NLA/PCNA Guideline on the Management of Blood Cholesterol. //: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2019;73:e285-e350. https://doi.org/10.1016/j.jacc.2018.11.003
6. Hoogeveen RC, Ballantyne CM. Residual Cardiovascular Risk at Low LDL: Remnants, Lipoprotein(a), and Inflammation. Clin Chem. 2021;67:143–53. https://doi.org/10.1093/clinchem/hvaa252.
7. Raposeiras-Roubin S, Rosselló X, Oliva B, Fernández-Friera L, Mendiguren JM, Andrés V, Bueno H, Sanz J, de Martínez V, Abu-Assi E, et al. Triglycerides and Residual Atherosclerotic Risk. J Am Coll Cardiol. 2021;77:3031–41. https://doi.org/10.1016/j.jacc.2021.04.059.
8. Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421.
9. Shiffman D, Louie JZ, Caulfield MP, Nilsson PM, Devlin JJ, Melander O. LDL subfractions are associated with incident cardiovascular disease in the Malmö Prevention Project Study. Atherosclerosis. 2017;263:287–92. https://doi.org/10.1016/j.atherosclerosis.2017.07.003.
10. Zhou P, Liu J, Wang L, Feng W, Cao Z, Wang P, Liu G, Sun C, Shen Y, Wang L, et al. Association of Small Dense Low-Density Lipoprotein Cholesterol with Stroke Risk, Severity and Prognosis. J Atheroscler Thromb. 2020;27:1310–24. https://doi.org/10.5551/jat.53132.
11. Higashioka M, Sakata S, Honda T, Hata J, Shibata M, Yoshida D, Goto K, Kitazono T, Osawa H, Ninomiya T. The Association of Small Dense Low-Density Lipoprotein Cholesterol and Coronary Heart Disease in Subjects at High Cardiovascular Risk. J Atheroscler Thromb. 2021;28:79–89. https://doi.org/10.5551/jat.55350.

12. Hoogeveen RC, Gaubatz JW, Sun W, Dodge RC, Crosby JR, Jiang J, Couper D, Virani SS, Kathiresan S, Boerwinkle E, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study. Arterioscler Thromb Vasc Biol. 2014;34:1069–77. https://doi.org/10.1161/atvbaha.114.303284.
13. Tsai MY, Steffen BT, Guan W, McClelland RL, Warnick R, McConnell J, Hoefner DM, Remaley AT. New automated assay of small dense low-density lipoprotein cholesterol identifies risk of coronary heart disease: the Multi-ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2014;34:196–201. https://doi.org/10.1161/atvbaha.113.302401.
14. Ikezaki H, Lim E, Cupples LA, Liu CT, Asztalos BF, Schaefer EJ. Small Dense Low-Density Lipoprotein Cholesterol Is the Most Atherogenic Lipoprotein Parameter in the Prospective Framingham Offspring Study. J Am Heart Association. 2021;10:e019140. https://doi.org/10.1161/jaha.120.019140.
15. Hirayama S, Miida T. Small dense LDL: An emerging risk factor for cardiovascular disease. Clin Chim Acta. 2012;414:215–24. https://doi.org/10.1016/j.cca.2012.09.010.
16. Burns SF, Lee SJ, Arslanian SA. Surrogate lipid markers for small dense low-density lipoprotein particles in overweight youth. J Pediatr. 2012;161:991–6. https://doi.org/10.1016/j.jpeds.2012.06.013.
17. Cho Y, Kim Y, Kim JH, Jee SH, Han K. The plasma small dense LDL-cholesterol calculation formula proposed by Srisawasdi et al is not applicable to Koreans who are healthy or have metabolic syndrome. Am J Clin Pathol. 2012;138:754–5. https://doi.org/10.1309/ajcpkkogej86lgju. author reply 756.
18. Sampson M, Wolska A, Warnick R, Lucero D, Remaley AT. A New Equation Based on the Standard Lipid Panel for Calculating Small Dense Low-Density Lipoprotein-Cholesterol and Its Use as a Risk-Enhancer Test. Clin Chem. 2021;67:987–97. https://doi.org/10.1093/clinchem/hvab048.
19. Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. Circulation. 2014;129:570–9. https://doi.org/10.1161/circulationaha.113.005757.
20. Wu Z, Zhou D, Liu Y, Li Z, Wang J, Han Z, Miao X, Liu X, Li X, Wang W, et al. Association of TyG index and TG/HDL-C ratio with arterial stiffness progression in a non-normotensive population. Cardiovasc Diabetol. 2021;20:134. https://doi.org/10.1186/s12933-021-01330-6.
21. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43:61–8. https://doi.org/10.1093/ije/dys203.
22. Vesper HW, Wilson PW, Rifai N. A message from the laboratory community to the National Cholesterol Education Program Adult Treatment Panel IV. Clin Chem. 2012;58:523–7. https://doi.org/10.1373/clinchem.2011.178202.
23. Miller WG, Myers GL, Sakurabayashi I, Bachmann LM, Caudill SP, Dziekonski A, Edwards S, Kimberly MM, Korzun WJ, Leary ET, et al. Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures. Clin Chem. 2010;56:977–86. https://doi.org/10.1373/clinchem.2009.142810.
24. Langlois MR, Descamps OS, van der Laarse A, Weykamp C, Baum H, Pulkki K, von Eckardstein A, De Bacquer D, Borén J, Wiklund O, et al. Clinical impact of direct HDLc and LDLc method bias in hypertriglyceridemia. A simulation study of the EAS-EFLM Collaborative Project Group. Atherosclerosis. 2014;233:83–90. https://doi.org/10.1016/j.atherosclerosis.2013.12.016.
25. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA et al. /ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082-e1143. https://doi.org/10.1161/cir.0000000000000625
26. Tall AR, Thomas DG, Gonzalez-Cabodevilla AG, Goldberg IJ. Addressing dyslipidemic risk beyond LDL-cholesterol. J Clin Investig. 2022;132. https://doi.org/10.1172/jci148559.
27. Quispe R, Martin SS, Michos ED, Lamba I, Blumenthal RS, Saeed A, Lima J, Puri R, Nomura S, Tsai M, et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. Eur Heart J. 2021;42:4324–32. https://doi.org/10.1093/eurheartj/ehab432.
28. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-Rich Lipoprotein Cholesterol, Small Dense LDL Cholesterol, and Incident Cardiovascular Disease. J Am Coll Cardiol. 2020;75:2122–35. https://doi.org/10.1016/j.jacc.2020.02.059.
29. Higashioka M, Sakata S, Honda T, Hata J, Yoshida D, Hirakawa Y, Shibata M, Goto K, Kitazono T, Osawa H, et al. Small Dense Low-Density Lipoprotein Cholesterol and the Risk of Coronary Heart Disease in a Japanese Community. J Atheroscler Thromb. 2020;27:669–82. https://doi.org/10.5551/jat.51961.
30. Sekimoto T, Koba S, Mori H, Sakai R, Arai T, Yokota Y, Sato S, Tanaka H, Masaki R, Oishi Y, et al. Small Dense Low-Density Lipoprotein Cholesterol: A Residual Risk for Rapid Progression of Non-Culprit Coronary Lesion in Patients with Acute Coronary Syndrome. J Atheroscler Thromb. 2021;28:1161–74. https://doi.org/10.5551/jat.60152.
31. Ishii J, Kashiwabara K, Ozaki Y, Takahashi H, Kitagawa F, Nishimura H, Ishii H, Iimuro S, Kawai H, Muramatsu T, et al. Small Dense Low-Density Lipoprotein Cholesterol and Cardiovascular Risk in Statin-Treated Patients with Coronary Artery Disease. J Atheroscler Thromb. 2021. https://doi.org/10.5551/jat.63229.
32. Siddiqui MB, Arshad T, Patel S, Lee E, Albhaisi S, Sanyal AJ, Stravitz RT, Driscoll C, Sterling RK, Reichman T, et al. Small Dense Low-Density Lipoprotein Cholesterol Predicts Cardiovascular Events in Liver Transplant Recipients. Hepatology (Baltimore MD). 2019;70:98–107. https://doi.org/10.1002/hep.30518.
33. Li G, Wu HK, Wu XW, Cao Z, Tu YC, Ma Y, Wang WQ, Cheng J, Zhou ZH. Small dense low density lipoprotein-cholesterol and cholesterol ratios to predict arterial stiffness progression in normotensive subjects over a 5-year period. Lipids Health Dis. 2018;17:27. https://doi.org/10.1186/s12944-018-0671-2.
34. Yang X, Li J, Hu D, Chen J, Li Y, Huang J, Liu X, Liu F, Cao J, Shen C, et al. Predicting the 10-Year Risks of Atherosclerotic Cardiovascular Disease in Chinese Population: The China-PAR Project (Prediction for ASCVD Risk in China). Circulation. 2016;134:1430–40. https://doi.org/10.1161/circulationaha.116.022367.
35. Hailili G, Chen Z, Tian T, Fu WH, Pei HL, Mahan Y, Luo T, Alimu D, Wang L, Zhang GZ, et al. Dietary patterns and their associations with the metabolic syndrome and predicted 10-year risk of CVD in northwest Chinese adults. Br J Nutr. 2021;126:913–22. https://doi.org/10.1017/s000711452000478x.
36. Xu Y, Li M, Qin G, Lu J, Yan L, Xu M, Wang T, Zhao Z, Dai M, Zhang D, et al. Cardiovascular Risk Based on ASCVD and KDIGO Categories in Chinese Adults: A Nationwide, Population-Based, Prospective Cohort Study. J Am Soc Nephrology: JASN. 2021;32:927–37. https://doi.org/10.1681/asn.2020060856.
37. Santos HO, Earnest CP, Tinsley GM, Izidoro LFM, Macedo RCO. Small dense low-density lipoprotein-cholesterol (sdLDL-C): Analysis, effects on cardiovascular endpoints and dietary strategies. Prog Cardiovasc Dis. 2020;63:503–9. https://doi.org/10.1016/j.pcad.2020.04.009.
38. Rizvi AA, Stoian AP, Janez A, Rizzo M. Lipoproteins and Cardiovascular Disease: An Update on the Clinical Significance of Atherogenic Small, Dense LDL and New Therapeutical Options. Biomedicines. 2021;9. https://doi.org/10.3390/biomedicines9111579.
39. Ivanova EA, Myasoedova VA, Melnichenko AA, Grechko AV, Orekhov AN. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. Oxidative Med Cell Longev. 2017;2017:1273042. https://doi.org/10.1155/2017/1273042.

Publisher's note