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Original Article

Twenty-year epidemiologic study on LDL-C levels in relation to the risks of atherosclerotic event, hemorrhagic stroke, and cancer death among young and middle-aged population in China

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KEYWORDS:
Low-density lipoprotein cholesterol;
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Hemorrhagic stroke;
Cancer;
Cohort study

BACKGROUND: Lowering elevated low-density lipoprotein cholesterol (LDL-C) levels is a key strategy in primary prevention of atherosclerotic cardiovascular disease (ASCVD), but the optimal LDL-C level is not well established in Chinese.

OBJECTIVE: We aimed to search for the LDL-C level that associated with the lowest long-term ASCVD risk without excess risk of other life-threatening diseases.

METHODS: Totally 20,954 participants aged 35–64 years were followed up for about 20 years. Cumulative and relative risks of ASCVD, hemorrhagic stroke, and cancer death, according to baseline LDL-C levels, were calculated using modified Kaplan-Meier and Fine & Gray models, considering competing risks. Preventable ASCVD cases against increased harms were estimated by simulation, replacing elevated LDL-C levels with lower LDL-C levels in the risk prediction models for individuals with different ASCVD risk.

RESULTS: The lower the baseline LDL-C, the lower the 20-year risk of ASCVD in participants with LDL-C levels ranging from the lowest category (<40 mg/dL) to the highest (≥160 mg/dL). We found no association between lower LDL-C levels and long-term risk of cancer death. If all people with LDL-C ≥130 mg/dL were assumed to have the LDL-C level <70 mg/dL and other risk factors remained unchanged, a substantial number of ASCVD cases would be preventable. However, for uncontrolled hypertensive patients, the LDL-C level <70 mg/dL would have extra harm from hemorrhagic stroke.

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CONCLUSION: Participants with baseline LDL-C <40 mg/dL had the lowest ASCVD risk. An excess risk of hemorrhagic stroke was observed in patients with uncontrolled hypertension and LDL-C <70 mg/dL. LDL-C 70–99 mg/dL had reasonably low ASCVD risk without excess risk of other life-threatening diseases.
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Introduction

A current feature of cardiovascular disease (CVD) epidemics in China is the rapid increase in premature deaths from atherosclerotic cardiovascular disease (ASCVD).[1,2] Lowering elevated low-density lipoprotein cholesterol (LDL-C) in a defined population is an important strategy in primary and secondary prevention of ASCVD that has strong evidence.[3–9]

However, it is not well established in primary prevention what is the optimal low LDL-C level with a lowest ASCVD risk but with no excess risk for other life-threatening diseases. Among 9 large randomized controlled trials (RCTs) evaluating the effect and safety of lowering LDL-C levels using statins in primary prevention of ASCVD,[10] participants in 4 trials reached an LDL-C <100 mg/dL, and those in 1 trial reached an LDL-C <70 mg/dL with a 2-year observation time.[11] The ECAD (Eliminate Coronary Artery Disease) trial launched in 2014 is a 10-year ongoing RCT study to test whether incident ASCVD events are more effectively prevented using statin-based LDL-C–lowering drugs compared with guideline-based treatment in healthy young to middle-aged adults, as primary prevention for ASCVD, with a target of LDL-C of 80 mg/dL for the treatment group.[12] To date, no RCTs or observational studies have reported an association between very low LDL-C levels (<70 mg/dL or <40 mg/dL) and the long-term risk of ASCVD in Chinese populations. Moreover, 2 meta-analyses of the Cholesterol Treatment Trialists' (CTT) Collaboration have suggested the possibility that lowering the LDL-C levels increases the risk of hemorrhagic stroke.[13,14] One of the CTT meta-analysis reported that if two trials, SPARCL and CORONA, were added to the RCTs included of this CTT meta-analysis, the risk of hemorrhagic stroke increased significantly by 21% (rate ratio: 1.21, 95% confidence interval [CI]: 1.05-1.41) per 1.0 mmol/L LDL-C reduction.[13] Furthermore, 2 meta-analyses of long-term cohort studies also showed that low baseline LDL-C or total cholesterol levels are associated with increased hemorrhagic stroke risk.[15,16] With respect to cancer, a meta-analysis of CTT Collaboration and 2 RCTs with an extended observation time showed that lowering LDL-C levels did not increase the risk of cancer.[10,17,18] Observational studies with generally longer observation times have showed inconsistent results in the populations with low baseline LDL-C levels.[19,20] No previous observational studies have investigated whether baseline LDL-C <70 mg/dL is positively associated with a long-term risk of either hemorrhagic stroke or cancer, 2 life-threatening diseases common among Chinese people.

Therefore, we aimed to examine the association between a wide spectrum of baseline LDL-C levels and the 20-year risks of ASCVD, hemorrhagic stroke, and cancer death in young and middle-aged Chinese without CVD at baseline, to determine the optimal LDL-C level for these populations in primary prevention, according to the lowest ASCVD risk without excess risk of hemorrhagic stroke or cancer death.

Material and methods

Study participants

The participants in this study were from the China Multi-Provincial Cohort Study, a nationwide, multicenter cohort study on determinants of CVD. This study included 16,810 participants aged 35–64 years who were free of CVD at baseline, recruited from 10 centers in 1992. In addition, this study also included 3126 participants recruited from 1996 to 1999, and 1361 participants recruited in 2004, aged 35–64 years and free of CVD at baseline. A multistage sampling method was used during enrollment. First, the centers were selected nonrandomly. Stratified random sampling for each sex and 10-year age group was then performed at each center for the baseline survey. The detailed methodology of the sampling procedure has been described in a previous publication.[21]

All methods for the baseline survey were in accordance with the World Health Organization–Monitoring of Trends and Determinants in Cardiovascular Disease protocol.[22] Informed consent was obtained from all participants. This present study was approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University (approval number: 2017025X).

All participants in this study underwent a follow-up every 1 to 2 years from the date of baseline examination, through 31 December 2013; the follow-up rate was 81.0%. A total of 21,297 Chinese participants aged 35–64 years without CVD were initially included. We excluded 13 (0.06%) participants with incomplete baseline data and 330 (1.5%) with triglyceride (TG) ≥400 mg/dL, for whom LDL-C levels could not be accurately estimated using the Friedewald formula.[23] Finally, a total of 20,954 participants were included in this study (Supplemental Fig. 1).

Risk factor measurement at baseline

Information on demographics, smoking status, alcohol consumption, family history of CVD, antihypertensive treatment, and lipid-lowering medication was collected using

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