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Original article

Both low and high levels of low-density lipoprotein cholesterol are risk factors for diabetes diagnosis in Chinese adults

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ABSTRACT

Aims: This study aimed to investigate whether both high and low levels of low-density lipoprotein cholesterol (LDL-C), *i.e.*, hypercholesterolemia and hypocholesterolemia, were associated with diabetes in Chinese adults.
Methods: This cross-sectional study included 22,557 Chinese adults. The LDL-C reference interval was determined from a healthy sub-cohort. Associations between hypocholesterolemia or hypercholesterolemia with diabetes were analyzed using binary logistic regression.
Results: The LDL-C reference interval was 1.48−3.77 mmol/L (57.23−145.78 mg/dL). Therefore, hypocholesterolemia, normocholesterolemia, and hypercholesterolemia were defined as an LDL-C concentration of <1.48, 1.48−3.77, and >3.77 mmol/L, respectively. Prevalence of diabetes was higher in people with hypocholesterolemia or hypercholesterolemia than that in people with normocholesterolemia. Hypocholesterolemia was associated with an increased multivariable-adjusted risk for diabetes diagnosis (odds ratio, 1.57; 95% confidence interval, 1.18−2.08), and so was hypercholesterolemia (odds ratio, 1.29; 95% confidence interval, 1.10−1.51). The results remained significant after exclusion of those who took lipid-lowering drugs from the analysis.
Conclusions: This study demonstrated that both low and high levels of LDL-C were associated with a higher risk of diabetes diagnosis. Patients with either high or low LDL-C may need to be closely monitored for the risk of diabetes .

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1. Introduction

Diabetes is one of the most pressing health concerns worldwide. Accumulating data from statin therapy, genetic studies, cross-sectional and longitudinal studies show that lower circulating levels of low-density lipoprotein cholesterol (LDL-C) are associated with a risk of higher prevalence and incidence of diabetes [1−6], raising concerns about statin therapy in diabetic patients who frequently have high circulating LDL-C.

On the other hand, a few studies showed that lower LDL was associated with a lower risk of diabetes. For example, pitavastatin, an LDL-C lowering drug, has been reported to improve glycemic control [7] and to decrease the risk of new-onset diabetes [8]. In addition, genetic studies revealed that some genetic variants that are associated with lower circulating LDL-C were associated with a lower risk of type 2 diabetes [6,9].

A possible explanation for the inconsistent reports is that both hypocholesterolemia (LDL-C below the lower boundary of its

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reference interval) and hypercholesterolemia (LDL-C above the upper boundary of its reference interval) may be associated with diabetes. To test this hypothesis, a reference interval for LDL-C is needed, as it can vary among people from different countries, even among people from different locations within the same country [10]. For example, reference intervals of LDL-C were reported to be 1.06−4.56 and 1.55 −4.77 mmol/L for Turkish regions of Denizli and Izmir, respectively [10].

This study aimed to determine the reference interval of LDL-C using a healthy sub-cohort of participants and then investigated the associations between hypocholesterolemia and diabetes or between hypercholesterolemia and diabetes.

2. Methods

2.1. Participants

A total of 22,571 participants underwent a routine health examination between January and May 2019 at the Health Physical Examination centre of the First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong Province, China. Thirteen participants were excluded due to being younger than 18 years and another one was excluded due to missing blood pressure data. The remaining 22,557 adult participants were included in this study. This retrospective study complied with the Declaration of Helsinki as revised in 2008 and was approved, and the requirement for obtaining patient informed consent was waived, by the Research Ethics Committee of the First Affiliated Hospital of Shandong First Medical University.

2.2. Fasting plasma glucose and definition of diabetes

Venous blood samples were collected after overnight fasting. Fasting plasma glucose was measured using the Olympus AU2700 automatic biochemical analyzer. Diabetes was defined as fasting blood glucose ≥7 mmol/L or treatment of diabetes [11].

2.3. Selection of a healthy sub-cohort of participants

To determine the reference interval of LDL-C, a healthy sub-cohort was selected from the whole cohort by excluding the following condition: diabetes, hypertension, presence of dyslipidemia, obesity, liver dysfunction, and renal dysfunction. Detailed definitions of the excluded conditions are listed below:

- diabetes was defined as fasting blood glucose ≥7 mmol/L or treatment of diabetes [11];
- hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or treatment of hypertension [12,13];
- dyslipidemia was defined according to 2016 Chinese guidelines for the management of dyslipidemia in adults [14] as any of the following: (a) triglycerides ≥2.3 mmol/L, or (b) total cholesterol ≥6.2 mmol/L, or (c) high-density lipoprotein cholesterol <1 mmol/L, or (d) treatment with lipid-lowering drugs;
- obesity was defined as body mass index ≥30 kg/m^2;
- liver dysfunction was defined as aspartate transaminase >40 IU/L [15]; and
- kidney dysfunction was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 [16].

2.4. Reference interval determination

The lower and upper reference intervals of LDL-C were determined at the 2.5th and 97.5th percentile using the healthy sub-cohort selected as per Section 2.3 [17].

2.5. Statistical analyses

All statistical analyses were performed using SPSS version 27.0 (IBM SPSS Statistics for Windows, Armonk, NY, International Business Machines Corporation). Continuous variables were presented as median and interquartile range and categorical variables were presented as number (percentage). The differences in continuous variables among multiple groups were analyzed using Kruskal-Wallis 1-way ANOVA followed by all pairwise posthoc tests [18]. The age-adjusted difference in fasting plasma glucose among groups was analyzed using the univariate general linear model with age as a covariate followed by least-squares posthoc tests. Differences among categorical variables were analyzed using Pearson's chi-square test. The associations of hypocholesterolemia or hypercholesterolemia with diabetes were analyzed using binary logistic regression, with or without adjustment for diabetes risk factors (age, obesity, and hypertension status) [19–21] and confounding factors related to LDL-C (sex, aspartate transaminase, and use of lipid-lowering drugs) [22]. Age, fasting plasma glucose, LDL-C, body mass index (BMI), and aspartate transaminase were natural log-transformed to improve data distribution before being put into the regression model [23]. In sub-analyses, participants who were taking lipid-lowering medications were excluded. All tests were two-sided and a P value of < 0.05 was regarded as statistically significant.

2.6. Data availability

All data from this article are available from the corresponding authors upon request.

3. Results

3.1. Reference interval of LDL-C in healthy participants

A total of 10,843 participants (4934 males) were classified as healthy. The reference interval (2.5th−97.5th percentiles) of LDL-C in this healthy sub-cohort was 1.48−3.77 mmol/L (57.23−145.78 mg/dL). Therefore, hypocholesterolemia, normocholesterolemia, and hypercholesterolemia in this study were defined as an LDL-C concentration of <1.48, 1.48−3.77, and >3.77 mmol/L, respectively.

3.2. Clinical characteristics of the cohort

The whole cohort included 22,557 participants aged 18−95 years with a median [interquartile range] age of 44 [33−55] years, among which 581, 20,263, and 1713 had low, normal, and high LDL-C (*i.e.*, hypocholesterolemia, normocholesterolemia, or hypercholesterolemia), respectively (Table 1). The characteristics of the cohort are shown in Table 1.

The prevalence of diabetes was higher in people with hypocholesterolemia (12.4%) or hypercholesterolemia (14.3%) compared with that in those with normocholesterolemia (8.2%, Table 1). The non-adjusted fasting plasma glucose level was higher in participants with hypercholesterolemia compared with that in those with normocholesterolemia (Table 1). After adjustment for age, the fasting plasma glucose level was also higher in participants with hypocholesterolemia compared with that in those with normocholesterolemia (mean [standard error]: 5.49 [0.05] mmol/L for hypocholesterolemia versus 5.37 [0.01] mmol/L for normocholesterolemia, $P = 0.026$).

3.3. Hypocholesterolemia and hypercholesterolemia were associated with diabetes diagnosis

Hypocholesterolemia was associated with a higher prevalence of diabetes (odds ratio [OR], 1.58; 95% confidence interval, 95% [CI], 1.23 −2.04; Table 2) and so was hypercholesterolemia (OR, 1.87; 95% CI,

Table 1
Clinical characteristics of the study participants stratified by the LDL cholesterol levels.

	Hypocholesterolemia	Normocholesterolemia	Hypercholesterolemia	All participants
LDL-C, median (IQR), mmol/L	1.30 (1.15–1.40)*	2.66 (2.25–3.08)	4.09 (3.91–4.36)*	2.70 (2.25–3.19)
Sample size, N (%, males)	581 (60.6)	20,263 (59.1)	1713 (56.6)	22,557 (59.0)
Age, median (IQR), y	40 (31–57)	43 (33–54)	53 (42–61)*	44 (33–55)
FPG, median (IQR), mmol/L	5.02 (4.71–5.61)	5.06 (4.74–5.48)	5.30 (4.91–5.85)*	5.08 (4.75–5.51)
AST, median (IQR), IU/L	18.5 (15.7–22.6)	18.5 (15.9–22.1)	19.9 (17.3–23.5)*	18.6 (16.0–22.2)
BMI, median (IQR), kg/m^2	23.8 (21.1–26.8)*	24.6 (22.3–27.0)	25.6 (23.4–27.8)*	24.7 (22.3–27.1)
Participants with lipid-lowering drugs, N (%)	8 (1.4)	238 (1.2)	34 (2.0)*	280 (1.2)
Diabetes, N (%)	72 (12.4)*	1663 (8.2)	245 (14.3)*	1980 (8.8)
Hypertension, N (%)	169 (29.1)	6039 (29.8)	787 (45.9)*	6995 (31.0)

Abbreviations: AST, Aspartate transaminase; BMI, body mass index; FPG, fasting plasma glucose; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; N, number.
* $P<0.05$ compared with those with normocholesterolemia (defined as LDL-C between 1.48 and 3.77 mmol/L).

Table 2
OR (95% CI) of risk for diabetes according to LDL-C category in 22,557 participants.

Models	Hypocholesterolemia OR (95% CI)	Normocholesterolemia [a] OR	Hypercholesterolemia OR (95% CI)
Model 1	1.58 (1.23–2.04)	1	1.87 (1.62–2.16)
Model 2	1.53 (1.17–2.00)	1	1.31 (1.13–1.52)
Model 3	1.57 (1.18–2.08)	1	1.29 (1.10–1.51)

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.
[a] Normocholesterolemia was defined as LDL-C between 1.48 and 3.77 mmol/L.
Model 1: Not adjusted.
Model 2: Adjusted for age.
Model 3: Adjusted for age, sex, body mass index, hypertension, aspartate transaminase, and use of lipid-lowering drugs.

Table 3
OR (95% CI) of risk for diabetes according to LDL-C category in 22,277 participants without lipid-lowering drugs.

Models	Hypocholesterolemia OR (95% CI)	Normocholesterolemia[a] OR	Hypercholesterolemia OR (95% CI)
Model 1	1.61 (1.24–2.10)	1	1.88 (1.62–2.20)
Model 2	1.53 (1.15–2.03)	1	1.31 (1.12–1.53)
Model 3	1.53 (1.15–2.05)	1	1.30 (1.11–1.53)

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio. A total of 280 participants who took lipid-lowering drugs were excluded and the remaining 22,277 participants were included in the analysis.
[a] Normocholesterolemia was defined as LDL-C between 1.48 and 3.77 mmol/L.
Model 1: Not adjusted.
Model 2: Adjusted for age.
Model 3: Adjusted for age, sex, body mass index, hypertension, and aspartate transaminase.

1.62–2.16). The associations remained statistically significant after adjustment for certain diabetes risk factors, such as age, BMI, and hypertension, as well as confounding factors related to LDL-C including sex, blood aspartate transaminase level, and the use of lipid-lowering drugs (Table 2). Sensitivity analyses showed that exclusion of those who used lipid-lowering drugs did not materially change the results (Table 3).

4. Discussion

This study was the first to investigate the associations between hypocholesterolemia and diabetes and between hypercholesterolemia and diabetes simultaneously in a single study, and found that both hypocholesterolemia and hypercholesterolemia were risk factors of diabetes diagnosis in Chinese adults.

The mechanisms underlying the association between hypocholesterolemia or hypercholesterolemia with diabetes are not known. Cholesterol seems to play an important role in regulating insulin secretion in pancreatic beta cells. Pharmacological inhibition of cholesterol biosynthesis in pancreatic islet cells led to impaired insulin secretion, which was reversed by cholesterol repletion [24]. On the other hand, a high concentration of LDL-C (6.2 mmol/L) reduced insulin secretion and β-cell proliferation and induced apoptosis of cultured beta cells [25]. Whether these mechanisms observed in vitro play an important role in vivo needs to be investigated in the future.

Hypocholesterolemia has been reported to be associated with diabetes from individuals of European ancestry in a cross-sectional study [2]. Our results extended this observation to a Chinese population.

A large proportion of older people often have both hypercholesterolemia and diabetes. However, to the best of our knowledge, whether hypercholesterolemia is an independent risk factor for diabetes is not well established. The current study suggested that hypercholesterolemia might be an independent risk factor for diabetes. However, this study only adjusted for limited factors including age, sex, body mass index, hypertension, aspartate transaminase, and use of lipid-lowering drugs. Future research needs to investigate whether hypercholesterolemia predicts diabetes after adjustment for other factors such as waist-to-hip ratio, liver fat content, and family history of diabetes.

The prevalence of use of lipid-lowering drugs in the hypercholesterolemia group was low (2%). The exact reason for this is not clear. This observation might, at least in part, be explained by the following reasons: 1) Relatively healthy condition of the participants. The participants in this study underwent a routine health examination and they were not those who were attending a clinic for some apparent symptoms or diseases. 2) Relatively low LDL cholesterol in the hypercholesterolemia group. Seventy-five percent (75%) of the participants

in this group had an LDL cholesterol level of ≤ 169 mg/dL. The high LDL cholesterol cut-off value for adult Chinese is 160 mg/dL [14]. 3) Some participants with high LDL cholesterol might not know they had the condition. 4) Some participants, who were aware of their condition of high LDL cholesterol, might refuse to take medicine.

Our observation that hypercholesterolemia was a risk factor for diabetes indicates that statin therapy in people with hypercholesterolemia may have a beneficial effect in protecting against diabetes. Indeed, pitavastatin, a non-potent LDL-C lowering drug, decreased the risk of new-onset diabetes in patients with such a condition [8]. However, when LDL-C is lowered to a level below its reference interval, the risk of diabetes may increase as this study and others [2] showed that hypocholesterolemia was a risk factor for diabetes. Indeed, the JUPITER study, in which the LDL-C concentrations in half of the participants were lowered below 1.4 mmol/L (lower than the lower boundary of our reference interval), showed that statin therapy increased the risk of new-onset diabetes by 26% in 2 years [4,26]. Therefore, our study suggests that both circulating glucose and LDL-C levels should be closely monitored in patients on statin therapy.

Our study might help to explain the inconsistent results from mendelian randomization studies. Some studies revealed that certain genetic variants that are associated with lower circulating LDL-C were associated with a higher risk of type 2 diabetes, whereas other variants that are associated with lower circulating LDL-C were associated with a lower risk of type 2 diabetes [6,9]. According to our observation that both hypocholesterolemia and hypercholesterolemia could be risk factors for diabetes, a possible explanation for these "inconsistent" observations in these Mendelian randomization studies is that those favorable LDL-C lowering variants may more frequently appear in people with high LDL-C and those unfavorable LDL-C lowering variants may more frequently appear in people with low LDL-C. This hypothesis needs to be investigated in the future.

This study had a number of strengths. Firstly, it had a large sample size. Secondly, abnormal LDL-C was defined using a reference interval that was determined from a large number of healthy participants selected from the whole cohort. This study also had several limitations. Firstly, it was based on cross-sectional data; therefore, a causal relationship between hypocholesterolemia or hypercholesterolemia and diabetes cannot be inferred. Secondly, information on the type of diabetes was not available. Thirdly, family history of diabetes, diet, physical activity, smoking, income, and marital status were not considered which could affect diabetes diagnosis [19]. Fourthly, this study was conducted in a Chinese cohort from a single hospital and the findings from this study may not be generalizable to all Chinese or people from other countries.

In conclusion, this study found that both hypocholesterolemia and hypercholesterolemia were independent risk factors for diabetes diagnosis. This study suggests that patients with either high or low LDL-C need to be closely monitored for the risk of diabetes.

Author contributions

Conceptualization: Y.W., G.Y.; Methodology: T.Q., H.S., Q.X.; Formal analysis and investigation: Y.W., G.Y; Writing - original draft preparation: Y.W.; Writing - review and editing: Y.F., D.S., Z.C., G.Y., D.J.M., J.G.; Funding acquisition: G.Y., Y.W.; Resources: X.H., W.H., G. Z.; Supervision: G.Y., Y.W.

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Declarations of Competing Interest

None

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