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Relationship of small dense low-density lipoprotein cholesterol level with pre-diabetes and newly detected type 2 diabetes

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To evaluate the relationship of serum small dense low-density lipoprotein cholesterol (sdLDL-C) level with pre-diabetes (PD) and newly detected type 2 diabetes (NT2D) in a Chinese adults population, a cross-sectional study was conducted in 2022 from May 26 to September 17. Permanent residents at the age of 30–69 years who lived in two communities in Zhejiang Province, China, and participated in a community health checkup were selected as the survey objects. According to their fasting plasma glucose and glycosylated hemoglobin, the eligible subjects were divided into normal blood glucose group, PD group, and NT2D group. Logistic regression model was used to explore the effect of sdLDL-C level on PD and NT2D, and restricted cubic spline (RCS) was adopted to display the nonlinear dose-response relationship of sdLDL-C with the prevalence of PD and NT2D. A total of 3570 subjects were included with a median age of 58 (52, 64) years, and 58.7% (2097) were women. The prevalence of PD was 53.6% (1913 cases), and NT2D was 9.2% (327 cases). Logistic regression analysis showed that after controlling the confounding factors (including LDL-C), for every 0.1 mmol/L increase in sdLDL-C, the risk of developing PD and NT2D increased by 3.4% (*OR* = 1.034, 95%*CI*:1.002–1.067) and 15.7% (*OR* = 1.157, 95%*CI*: 1.097–1.220), respectively. The RCS curves showed that with the increase of sdLDL-C, both the risk of PD (*P* = 0.037) and NT2D (*P* < 0.001) increased, but there were no nonlinear dose-response relationships between sdLDL-C with PD (*P* for non-linearity = 0.142) and NT2D (*P* for non-linearity = 0.227). Subjects are at increased risk of PD and NT2D with increase of serum sdLDL-C level. sdLDL-C is a promising risk factor for PD and NT2D independent of LDL-C.

Keywords Small dense low-density lipoprotein cholesterol, Type 2 diabetes, Pre-diabetes, Restricted cubic spline

Abbreviations

sdLDL	small dense low-density lipoprotein
sdLDL-C	small dense low-density lipoprotein cholesterol
T2D	type 2 diabetes
PD	pre-diabetes
NT2D	newly detected type 2 diabetes
RCS	restricted cubic spline
LDL	low density lipoprotein
NCEP	National Cholesterol Education Program
EDTA	ethylenediaminetetraacetic acid
FBG	fasting blood glucose
TC	total cholesterol
TG	triglyceride
LDL-C	low-density lipoprotein cholesterol
HDL-C	high-density lipoprotein cholesterol
HbA1c	glycated hemoglobin A1c
WC	waist circumference

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SBP	systolic blood pressure
DBP	diastolic blood pressure
BMI	body mass index
CDC	Center for Disease Control and Prevention
NGT	normal glucose tolerance
OR	Odds Ratio
IR	insulin resistance
VLDL	very low density lipoprotein
GDM	gestational diabetes mellitus
CVD	cardiovascular diseases
ACS	acute coronary syndrome
CHD	Coronary Heart Disease
MTP	microsomal triglyceride transfer protein
GWAS	genome-wide association study
MDL	minimum detection limit
AMR	analytical measurement range

Type 2 diabetes (T2D) is a disorder syndrome of glucose metabolism caused by insulin resistance or islet dysfunction. Pre-diabetes (PD) is a state of abnormal glucose metabolism between normal blood glucose and diabetes. PD increases the risk of diabetes by 3–10 times[1]. With the change of lifestyle and the aggravation of population aging, the number of T2D and PD increased rapidly. The prevalence of T2D in Chinese adults increased from 10.9% in 2013 to 12.4% in 2018, the prevalence of PD increased from 35.7% in 2013 to 38.1% in 2018, with a total of more than 50% in the two groups and the highest number of patients in the world[2]. The medical and economic burden caused by T2D is increasing. Therefore, it is of great significance to actively prevent T2D and PD to reduce the incidence of related diseases and improve the quality of life.

Low density lipoprotein (LDL) consists of a group of quasi-spherical particles, heterogeneous in density, molecular weight, chemical composition, surface charge and size[3]. LDL particles with density greater than 1.034 g/mL and diameter less than 25.5 nm are collectively referred to as small and dense low density lipoprotein (sdLDL), and the cholesterol they carry is called small dense low-density lipoprotein cholesterol (sdLDL-C). A single increase in LDL-C level predicted only about a 50% risk of coronary heart disease[4], while sdLDL-C is considered to be one of the most atherogenic and most strongly predictive of cardiovascular events[5–7]. As an emerging risk factor associated with a variety of diseases, sdLDL-C has been included in the adult treatment group of the United States National Cholesterol Education Program (NCEP) committee as one of the newly discovered important cardiovascular risk factors.

However, the predictive value of sdLDL-C on glucose metabolism, diabetes, and even the risk of diabetes complications has not been thoroughly investigated. A study performed by Hoogeveen et al.[7] in 2014 indicated that plasma sdLDL-C levels were strongly correlated with an atherogenic lipid profile and were higher in patients with diabetes mellitus than non-diabetes mellitus (49.6 versus 42.3 mg/dL; $P < 0.0001$). A study in South Korea also found that diabetic patients had a smaller mean-LDL particle size and higher proportion of sdLDL compared to those of subjects without diabetes[8].

There have been several reports on blood lipid profiles and sdLDL levels in patients with type 2 diabetes and pre-diabetes in China, but generally the sample size is not very large, and some research subjects have received different treatments, which cannot reflect the real characteristics of blood lipid profiles. Therefore, this study selected participants with newly detected type 2 diabetes(NT2D), pre-diabetes(PD) and normal blood glucose, and conducted standardized questionnaire survey, physical examination and laboratory measurements to explore the distribution characteristics of serum sdLDL-C, so as to provide more reliable data for the risk and assessment of the progression from normal blood glucose to pre-diabetes and pre-diabetes to diabetes. At the same time, it provides a basis for the significance of sdLDL-C for the early prevention, early detection and early diagnosis of diabetes, a major public health problem.

Materials and methods

Participants

In 2022 from May 26 to September 17, a cross-sectional study was conducted. Permanent residents lived in two communities in Zhejiang Province, China, and participated in a community health examination were recruited. Inclusion criteria: 30–69 years old, consciousness, capable of completing the questionnaire independently, and free from mental illness. Subjects were excluded if they meet any of the following items during the survey period: ill in bed, schizophrenia, dementia, pregnant or lactating women.

This study was approved by the ethics committee of Zhejiang Provincial Center for Disease Control and Prevention(2020-040-01). Written informed consent was obtained from each participant. All methods, including biological specimen examination, anthropometric measurement and questionnaire surveys, were conducted according to relevant guidelines and regulations.

Methods

Blood samples collection

Three tubes of fasting venous blood samples were drawn from each participants: 2 mL sodium fluoride/potassium oxalate tube, 5 mL gel/clot activator serum tube and 2 mL ethylenediaminetetraacetic acid (EDTA) anticoagulant tube.

Performance validation of sdLDL-C kit[9,10]

A commercial kit (product code: BSBE GSSD/B) was used to measure sdLDL-C (peroxidase method). The sdLDL-C kit was firstly validated for performance by KingMed Diagnostics Co., LTD.

Accuracy verification: Reference material samples at two distinct concentrations of high and low were measured three times daily for five consecutive days. Mean values and biases were then calculated for each concentration.

Precision verification: Two serum samples (high and low sdLDL-C concentrations) were each measured three times within a single batch to calculate the intra-batch precision. The inter-batch precision was calculated after five consecutive days' measurement.

Linear range verification: Two serum samples (high and low sdLDL-C concentrations) were mixed in varying proportions to prepare six dilution levels. Each dilution was measured three times. The mean values (Y) were plotted against the degree of dilution of high concentration sample (X) for curve fitting and regression analysis.

Minimum detection limit (MDL): One serum sample was diluted with 5% bovine serum albumin saline solution to produce samples close to the manufacturer's stated MDL. Each sample was determinated 5 times. The means of the lowest concentration with a total error or uncertainty equal to or less than the expected value was defined as the MDL.

Maximum dilution factor: Three samples near the manufacturer's stated upper analytical measurement range (AMR) were diluted with normal saline to produce samples close to the manufacturer's stated upper linear range limit. Both undiluted and diluted samples were measured three times, and the bias of the restored concentration and undiluted concentration were used to determine the maximum reliable dilution factor.

Reportable range: The lower limit was defined as the higher value between the MDL and the lowest linear range concentration. The upper limit was calculated as (upper linear range limit) × (maximum dilution factor).

Blood samples measurements

Biochemical indexes were measured by automatic biochemical analyzer.

Fasting blood glucose (FBG, hexokinase method) was measured by using plasma samples in the sodium fluoride/potassium oxalate tubes.

Serum samples were provided for the measurements of sdLDL-C (peroxidase method), total cholesterol (TC; oxidase method), triglyceride (TG; enzymatic method), low-density lipoprotein cholesterol (LDL-C; direct clearance method), and high-density lipoprotein cholesterol (HDL-C; direct clearance method).

Blood samples in EDTA anticoagulant tubes were used to measure glycated hemoglobin A1c (HbA1c; high-performance liquid chromatography, automatic HbA1c analyzer).

All the measurements above should be conducted by KingMed Diagnostics Co., LTD on the same day as the blood samples were collected.

Data collection and medical examination

For the storage of data on standardized questionnaire survey, physical examination and laboratory measurements, an electronic survey system was developed. The standardized questionnaire survey was conducted by the electronic survey system through a face-to-face interview. Information as the followings were collected, social demographic characteristics such as age, gender, ethnicity, education level, etc.; behaviors and lifestyles such as smoking, drinking, tea and coffee, dietary, living environment, physical activity, etc.; personal and family health status such as history of major chronic diseases including diabetes, hyperlipidemia, hypertension and family history, medication use, etc.; sleep, mood, and mental health; history of female fertility; the family conditions such as family economy, fuel, heating, dietary, etc.

After at least 8 h of overnight fasting, physical examination was performed, including systolic blood pressure (SBP), diastolic blood pressure (DBP), height, fasting weight, fasting waist circumference (WC), etc. With an electronic sphygmomanometer (OMRON, Shanghai, China) which was accurate to 1 mmHg, SBP and DBP were measured two consecutive times (interval 1 min) on the right arm, and the mean value was taken. Height and weight were measured by a height and weight scale, which was accurate to 0.1 cm and 0.1 kg, respectively. A waist ruler which was accurate to 0.1 cm was used to measure WC.

All the results of blood samples' measurements and physical examination above should be uploaded to the electronic survey system on the same day.

Definition criteria

Newly detected T2D (NT2D): FBG ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5%, and self-reported no previous diagnosis of T2D. Pre-diabetes(PD): 6.1 mmol/L ≤ FBG < 7.0 mmol/L, and/or 5.7%≤ Hb1 Ac < 6.5%, and self-reported no previous diagnosis of type 2 diabetes[11].

Hypertension: SBP ≥ 140 mmHg; and/or DBP ≥ 90 mmHg; and/or who had previously been diagnosed with hypertension, according to 2018 Chinese guidelines for the management of hypertension[12].

Any of the following is defined as dyslipidemia: who had previously been diagnosed with dyslipidemia; and/or total cholesterol (TC) ≥ 5.2 mmol/L; and/or total triglyceride (TG) ≥ 1.70 mmol/L; and/or low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L; and/or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L, according to 2016 Chinese guideline for the management of dyslipidemia in adults[13].

Body mass index (BMI) = weight (kg)/(height (m) ^{2})[14].

Current smoking refers to smoking more than 1 cigarette per day for consecutive or cumulative 6 months.

Drinking is defined as a response of ≥1 time per week in the past year. Alcoholic beverages included beer, liquor, red wine, and rice wine.

Regullar physical activity is ≥150 min per week of moderate-intensity or a combination of moderate- and high-intensity exercise or ≥75 min per week of high-intensity exercise.

Quality control

The investigators were uniformly centralized trained and qualified before the survey. All the interviews and examinations were conducted following standardized protocols. A quality control team was established by both the provincial Center for Disease Control and Prevention (CDC) and on-site investigation groups, and was strict to quality control on-site investigation questionnaires, physical examination, laboratory measurements and information entry and so on.

Statistical analysis

Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R version 4.3.0 (http://www.R-project.org). The normal distribution data were described by x ± s, and *t* test and variance analysis were used for comparison between groups. The abnormal distribution data were represented by M (Q1, Q3), and non-parametric tests were used for comparison between groups. The χ^2 test and rank sum test were used for comparison between groups for categorical and rank variables, respectively. Logistic regression model was used to analyze the effect of sdLDL-C level on PD and newly detected T2D. Restricted cubic spline (RCS) curve was used to analyze the dose-response relationship between sdLDL-C level and PD and newly detected T2D (The reference value for sdLDL-C was the median overall sdLDL-C of 0.939 mmol/L, Knot = 4). P values < 0.05 were considered statistically significant. Furthermore, subgroup analyses were conducted to test for effect modification by age(≤ 55 or >55 years old) and gender on PD and NT2D. Interaction on the multiplicative scale was evaluated using likelihood ratio tests.

Results

Performance validation of sdLDL-C kit

Accuracy verification: Bias for the low-concentration reference material was -2.47%, and -1.50% for the high-concentration sample. Both values fell within the manufacturer's declared tolerance (≤ ±10% or ±3 mmol/L). Verification passed.

Precision verification: Intra-batch CVs were 2.53% (low concentration) and 5.15% (high concentration). Inter-batch CVs were 1.86% (low concentration) and 2.36% (high concentration). All CVs met manufacturer specifications (intra-batch ≤ 7.5% [1/4 TEA, TEA = 30%]; inter-batch ≤ 10.0% [1/3 TEA]). Verification passed.

Linear range verification: Linear range was 0.104–2.333 mmol/L (manufacturer claim: 0.104–2.590 mmol/L). Correlation equation was $Y = 2.239X + 0.113$, $R^2 = 0.9991$. Verification passed.

Minimum detection limit: measured MDL was 0.075 mmol/L (manufacturer claim: 0.104 mmol/L). Verification passed

Maximum dilution factor: After 3-fold dilution, biases were -6.14%, -3.95%, and -2.04% for the three samples and met the criterion of bias ≤ 1/2 TEA (CV ≤ 15%, TEA = 30%). Verification passed (maximum dilution factor = 3).

Reportable range: Lower limit was 0.104 mmol/L (the higher value between the MDL(0.075 mmol/L) and the lowest linear range concentration (0.104 mmol/L). Upper limit was 6.999 mmol/L (2.333 mmol/L × 3). The final reportable range was 0.104–6.999 mmol/L.

Validation data above confirmed that the sdLDL-C kit (peroxidase method) exhibits good performance in terms of accuracy, precision, and linearity. All measured values of our study fell within the kit's declared reportable range (0.104–6.999 mmol/L).

General characteristics

A total of 4222 subjects with complete survey data were obtained, 752 subjects with self-reported dyslipidemia and taking lipid-lowering drugs and self-reported diabetes were excluded, and 3570 subjects who met the inclusion and exclusion criteria were finally included.

Among the 3570 subjects, 2097 (58.7%) were females and 1473 (41.3%) were males, with an median age of 58 (52, 64) years. The number of NT2D and PD was 327 and 1913, respectively, with the detection rate of 9.2% and 53.6%. Compared with people with normal blood glucose, patients with NT2D and PD were older, more females, much higher prevalence of hypertension, much higher the proportion of less than 9 years of education, while much lower the proportion of smoking and drinking. Compared with people with normal blood glucose, patients with NT2D and PD had much higher BMI, WC, DBP, SBP, TC, LDL-C, TG, sdLDL-C, while much lower HDL-C concentration. The specific characteristics of the research subjects are shown in Table 1.

Basic information on quartile levels of sdLDL-C

The median sdLDL-C concentration of the 3570 subjects was 0.939 mmol/L. When the respondents were divided into four groups (Q1, Q2, Q3 and Q4) according to the quartiles of sdLDL-C, it was found that compared with Q1, the median ages of the subjects in the Q2, Q3 and Q4 groups were gradually increased, while there was no significant gender differences among Q1, Q2, Q3 and Q4 groups. The proportion of drinkers, and the prevalence of hypertension, NT2D and PD significantly increased with the increase of sdLDL-C concentration. Meanwhile,

Characteristics	All ($n=3570$)	Normal blood glucose ($n=1330$)	Pre-diabetes (PD) ($n=1913$)	Newly detected type 2 diabetes (NT2D) ($n=327$)	χ^2/H	*P* value
Age [years, $M(Q_1,Q_3)$]	58 (52, 64)	56(48, 62)	59(54, 64)	59(55, 65)	152.56	0.000**
TC [mmol/L, $M(Q_1,Q_3)$]	5.31 (4.67, 5.98)	5.06(4.46, 5.72)	5.44(4.79, 6.08)	5.52(4.93, 6.36)	122.46	0.000**
TG [mmol/L, $M(Q_1,Q_3)$]	1.41 (1.01, 2.09)	1.25(0.90, 1.87)	1.47(1.06, 2.12)	1.79(1.23, 2.83)	118.82	0.000**
HDL-C [mmol/L, $M(Q_1,Q_3)$]	1.41 (1.18,1.67)	1.45(1.21, 1.72)	1.40(1.18, 1.66)	1.28(1.09, 1.52)	55.30	0.000**
LDL-C [mmol/L, $M(Q_1,Q_3)$]	3.23 (2.66, 3.81)	3.00(2.51, 3.59)	3.33(2.75, 3.91)	3.46(2.85, 4.15)	113.56	0.000**
sdLDL-C [mmol/L, $M(Q_1,Q_3)$]	0.939 (0.682, 1.226)	0.848(0.619, 1.122)	0.972(0.713, 1.262)	1.139(0.855, 1.380)	137.55	0.000**
BMI [kg/m^2, $M(Q_1,Q_3)$]	23.4 (21.3, 25.6)	22.6(20.8, 24.8)	23.6(21.6, 25.9)	25.3(23.0, 27.8)	172.09	0.000**
WC [cm, $M(Q_1,Q_3)$]	84.1 (78.2, 90.1)	82.1(76.5, 88.1)	85.1(79.2, 90.6)	89.1(83.1, 96.1)	195.04	0.000**
SBP [mmHg, $M(Q_1,Q_3)$]	133 (121, 146)	129(118, 143)	134(122, 148)	140(128, 151)	94.12	0.000**
DBP [mmHg, $M(Q_1,Q_3)$]	84 (76, 90)	82(75, 90)	84(76, 90)	86(80, 93)	32.22	0.000**
Gender, *n(%)*					13.61	0.001**
Female	2097 (58.7)	730 (54.9)	1174 (61.4)	193 (59.0)		
Male	1473 (41.3)	600 (45.1)	739 (38.6)	134 (41.0)		
Ethnicity, *n(%)*					18.08	0.001**
Others	352 (9.9)	165 (12.4)	154 (8.1)	33 (10.1)		
Han	3218 (90.1)	1165 (87.6)	1759 (91.9)	294 (89.9)		
Education years, *n(%)*					29.31	0.000**
< 9	3256 (91.2)	1180 (88.7)	1767 (92.4)	309 (94.5)		
9–12	263 (7.4)	115 (8.6)	132 (6.9)	16 (4.9)		
≥ 12	51 (1.4)	35 (2.6)	14 (0.7)	2 (0.6)		
Hypertension,*n(%)*	1906 (53.4)	577 (43.4)	1090 (57.0)	239 (73.1)	114.405	0.000**
Family history of hypertension, *n(%)*	1434 (40.2)	533 (40.1)	770 (40.3)	131 (40.1)	0.012	0.994
Family history of diabetes, *n(%)*	57 (1.6)	21 (1.6)	28 (1.5)	8 (2.4)	1.721	0.423
Smoking, *n(%)*	667 (18.7)	278 (20.9)	331 (17.3)	58 (17.7)	6.903	0.032*
Drinking, *n(%)*	700 (19.6)	316 (23.8)	320 (16.7)	64 (19.6)	24.61	0.000**
Regullar physical activity, *n(%)*	129 (3.6)	50 (3.8)	68 (3.6)	11 (3.4)	0.159	0.924

Table 1. Demographic characteristics of the 3570 participants at different disease stages. *:*significance level*<0.05; **:*significance level*<0.01.

BMI, WC, DBP, SBP, TC, LDL-C, and TG also all increased with the increase of sdLDL-C concentration, while HDL-C showed a decreasing trend from Q1 to Q3, followed by a upward at Q4 (Table 2).

Correlation analysis of sdLDL-C with PD and NT2D

Binary logistic regression analyses were performed, taking the normal blood glucose participants as the control group, and the pre-diabetes (no = 0; yes = 1) and newly detected type 2 diabetes (no = 0; yes = 1) respectively as the dependent variable, and sdLDL-C as the independent variable. After adjusting for confounding variables (age, gender, education level, ethnicity, smoking, drinking, regullar physical activity, BMI, WC, hypertension, SBP, DBP and LDL-C), the results showed that for every 0.1 mmol/L increase in sdLDL-C concentration of the subjects, the risk of pre-diabetes increased by 3.4% (*OR* = 1.034, 95%*CI*:1.002–1.067), and the risk of newly detected type 2 diabetes increased by 15.7% (*OR* = 1.157, 95%*CI*:1.097–1.220)(Table 3).

Plot RCS with the references of the median sdLDL-C (0.939 mmol/L). After adjusting for age, gender, education level, ethnicity, smoking, drinking, regullar physical activity, BMI, WC, hypertension, SBP, DBP and LDL-C, the RCS model with four knots was used to analyze the relationships of the continuous change of sdLDL-C with pre-diabetes and newly detected type 2 diabetes. RCS curves showed that with the increase of sdLDL-C, both the risk of pre-diabetes ($P = 0.037$) and newly detected type 2 diabetes ($P < 0.001$) increased, while there was no nonlinear dose-response relationship between sdLDL-C level with pre-diabetes (*P* for non-linearity = 0.142) and newly detected type 2 diabetes (*P* for non-linearity = 0.227). (Figure. 1). Figure 2 exhibited the results of subgroup analyses. To PD, significant interaction of sdLDL-C levels was found across age(≤ 55 or >55 years old) while no significant interaction was found across gender; and to NT2D, significant interaction of sdLDL-C levels was found across gender while no significant interaction was found across age(≤ 55 or >55 years old).

Discussion

3B Research shows that 42% of the type 2 diabetics in China combined with dyslipidemia[15]. The predominant lipid abnormality in subjects with T2D is the lipid triad, which is an atherosclerotic lipoprotein phenotype manifested by hypertriglyceridemia, low HDL-C concentrations and elevated levels of sdLDL particles[16,17]. Studies have shown that compared with people with normal glucose tolerance (NGT), people with PD and NT2D are more likely to have dyslipidemia, mainly manifested as decreased HDL-C levels and increased TC, TG and non-HDL-C levels[18], and characterized by raised sdLDL-C levels[19,20]. Similar to the results of previous studies,

Characteristics	Q1 ($n = 894$)	Q2 ($n = 894$)	Q3 ($n = 891$)	Q4 ($n = 891$)	χ^2/H	*P* value
Age[years, $M(Q_1,Q_3)$]	58 (50, 64)	58 (52, 64)	58 (53, 64)	58 (53,64)	4.73	0.003**
TC [mmol/L, $M(Q_1,Q_3)$]	4.44 (3.95, 4.94)	5.07 (4.61, 5.53)	5.48 (5.06, 5.94)	6.32 (5.80, 6.86)	1765.32	0.000**
TG [mmol/L, $M(Q_1,Q_3)$]	0.92 (0.71, 1.20)	1.25 (0.99, 1.71)	1.65 (1.25, 2.28)	2.08 (1.57, 2.78)	1181.62	0.000**
HDL-C [mmol/L, $M(Q_1,Q_3)$]	1.54 (1.31, 1.82)	1.42 (1.19, 1.70)	1.32 (1.12, 1.56)	1.36 (1.15, 1.58)	184.86	0.000**
LDL-C[mmol/L, $M(Q_1,Q_3)$]	2.50 (2.08, 2.85)	3.06 (2.69, 3.42)	3.46 (2.97, 3.84)	4.10 (3.64, 4.55)	1794.00	0.000**
BMI [kg/m^2, $M(Q_1,Q_3)$]	22.3 (20.1, 24.6)	23.3 (21.3, 25.6)	23.6 (21.8, 25.8)	24.2 (22.3, 26.3)	177.65	0.000**
WC [cm, $M(Q_1,Q_3)$]	81.1 (75.1, 87.8)	84.1 (78.1, 89.6)	85.1 (79.2, 90.2)	87.1 (82.0, 92.1)	205.63	0.000**
SBP [mmHg, $M(Q_1,Q_3)$]	129 (116, 142)	132 (120, 146)	134 (122, 146)	137 (124, 150)	82.92	0.000**
DBP [mmHg, $M(Q_1,Q_3)$]	80 (74, 88)	82 (76, 90)	84 (77, 91)	86 (79, 93)	116.30	0.000**
Gender, *n(%)*					6.584	0.086
Female	374 (41.8)	356 (39.8)	347 (38.9)	396 (44.4)		
Male	520 (58.2)	538 (60.2)	544 (61.1)	495 (55.6)		
Ethnicity, *n(%)*					2.867	0.825
Others	92 (10.3)	89 (10.0)	78 (8.8)	93 (10.4)		
Han	802 (89.7)	805 (90.0)	813 (91.2)	798 (89.6)		
Education years, *n(%)*					9.440	0.150
< 9	817 (91.4)	804 (89.9)	824 (92.5)	811 (91.0)		
9–12	58 (6.5)	77 (8.6)	57 (6.4)	71 (8.0)		
≥ 12	19 (2.1)	13 (1.5)	10 (1.1)	9 (1.0)		
Blood glucose status, *n(%)*					131.595	0.000**
normal blood glucose	428 (47.9)	370 (41.4)	293 (32.9)	239 (26.8)		
pre-diabetes (PD)	426 (47.7)	464 (51.9)	500 (56.1)	523 (58.7)		
newly detected type 2 diabetes (NT2D)	40 (4.5)	60 (6.7)	98 (11.0)	129 (14.5)		
Hypertension, *n(%)*	400 (44.7)	451 (50.4)	487 (54.7)	568 (63.7)	68.968	0.000**
Family history of hypertension, *n(%)*	358 (40.0)	340 (38.0)	356 (40.0)	380 (42.6)	4.002	0.261
Family history of diabetes, *n(%)*	10 (1.1)	13 (1.5)	16 (1.8)	18 (2.0)	2.658	0.447
Smoking, *n(%)*	172 (19.2)	152 (17.0)	152 (17.1)	191 (21.4)	7.837	0.050
Drinking, *n(%)*	144 (16.1)	158 (17.7)	166 (18.6)	232 (26.0)	32.983	0.000**
Regullar physical activity, *n(%)*	36 (4.0)	32 (3.6)	28 (3.1)	33 (3.7)	1.030	0.794

Table 2. Basic information on quartiles of SdLDLC levels of the 3570 participants. Q1: sdLDLC < = 0.682 mmol/L; Q2: 0.682 mmol/L< sdLDLC < = 0.939 mmol/;Q3: 0.939 mmol/L< sdLDLC < = 1.226 mmol/L;4: sdLDLC > 1.226 mmol/L. *:*significance level*<0.05; **:*significance level*<0.01.

	Pre-diabetes (PD)			Newly detected type 2 diabetes (NT2D)		
Disease Stages	***β***	***P* value**	***OR* (95% *CI*)**	***β***	***P* value**	***OR* (95% *CI*)**
Model 1	0.077	0.000**	1.080 (1.059–1.101)	0.155	0.000**	1.168 (1.131–1.205)
Model 2	0.064	0.000**	1.066 (1.045–1.088)	0.132	0.000**	1.141 (1.103–1.180)
Model 3	0.065	0.000**	1.067 (1.046–1.089)	0.126	0.000**	1.134 (1.096–1.174)
Model 4	0.034	0.035*	1.034 (1.002–1.067)	0.146	0.000**	1.157 (1.097–1.220)

Table 3. Logistic regression analysis of sdLDL-C concentration and pre-diabetes and newly detected type 2 diabetes. Model 1: Adjusted for age, gender, ethnicity and education years. Model 2: Model 1 + Adjusted for smoking, drinking, regullar physical activity, BMI and WC. Model 3: Model 2 + Adjusted for hypertension, SBP, DBP. Model 4: Model 3 + Adjusted for LDLC. The odds ratio (*OR*) with its 95% confidence interval (*CI*) indicates that for every 0.1 mmol/L increase in sdLDL-C levels, the corresponding change in the risk of developing pre-diabetes (PD) or newly detected type 2 diabetes (NT2D). *:*significance level*<0.05; **:*significance level*<0.01.

the present study found that sdLDL levels, as well as TC, TG and LDL-C levels were significantly increased, while HDL-C levels were significantly decreased in people with PD and NT2D compared with those with normal blood glucose. Therefore, the lipid triad may be not only a manifestation of T2D, but also the lipid abnormalities characteristics of patients with NT2D and PD. The main causes of T2D are defective insulin secretion and a decrease in the function of insulin to accelerate the uptake and utilization of glucose in the body (i.e., insulin resistance(IR))[21]. Dyslipidemia is more likely to occur when glucose metabolism is abnormal, which may be

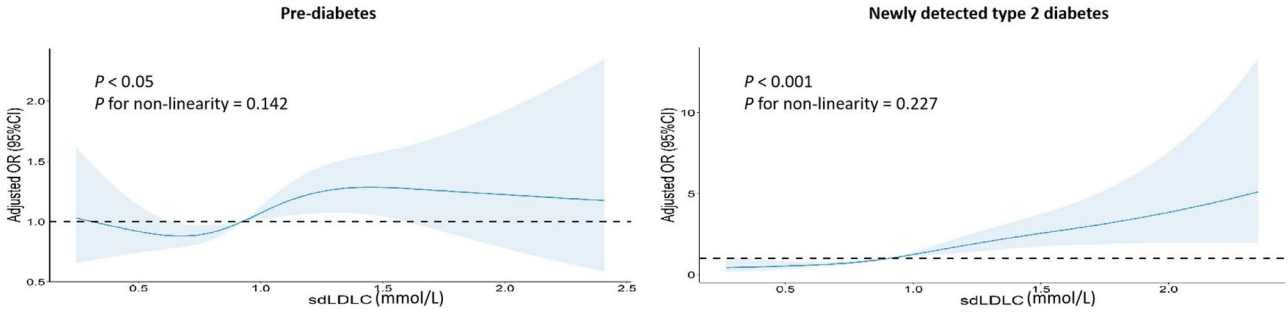

Fig. 1. The relationship between the continuous change of sdLDL-C and pre-diabetes and newly detected type 2 diabetes.

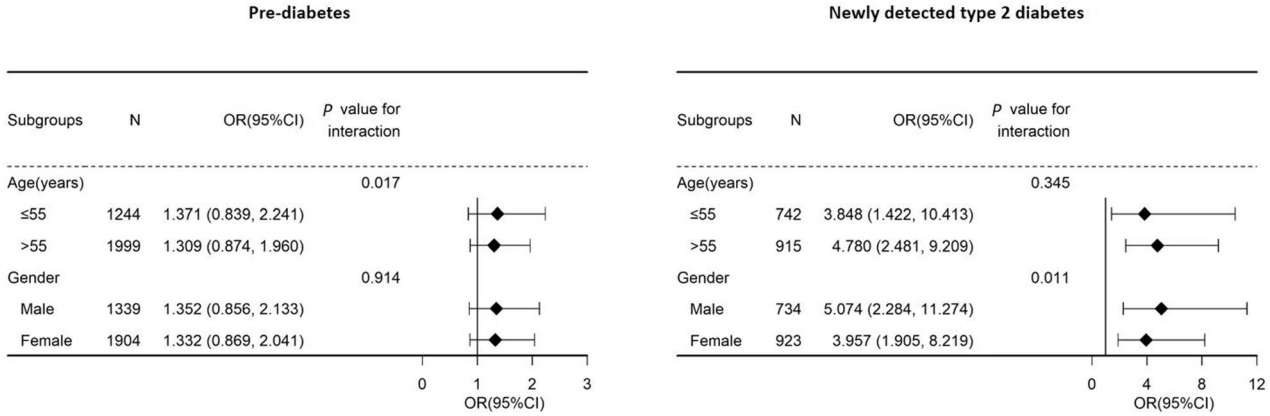

Fig. 2. Association between sdLDL-C levels and pre-diabetes/newly detected type 2 diabetes risk stratified by different factors (After adjusting for age, gender, education level, ethnicity, smoking, drinking, regullar physical activity, BMI, WC, hypertension, SBP, DBP and LDL-C).

related to the aggravation of IR. The formation of sdLDL is an important lipid metabolic transition in the context of insulin resistance. IR generates a series of effects including hyperinsulinemia. IR/hyperinsulinemia stimulates the increase of hepatic lipolysis and free fatty acid levels, and increases serum TG content and enhances the activity of microsomal triglyceride transfer protein (MTP). MTP plays a critical role in very low density lipoprotein (VLDL) assembly by facilitating the lipidation of apoB with TG[22]. The overproduction of VLDL1, driven by hepatic esterase and increased hepatic TG production, is a key metabolic abnormality in diabetic dyslipidemia[23], but IR/hyperinsulinemia does not affect the production of small, TG-poor VLDL2 particles[24]. As sdLDL particles are predominantly derived from VLDL1[3,25,26], the overproduction of VLDL1 plays a major role in elevating sdLDL levels. Therefore, in the case of insulin resistance, hyperglycemia eventually leads to increased TG, sdLDL levels and other dyslipidemia[27–29].

On the other hand, dyslipidemia is an important factor that promotes apoptosis of islet β-cells, insulin biosynthesis disorders, insulin secretion defects, and changes in glucose metabolism. Dyslipidemia increases the risk of PD and NT2D, in which the reduction of LDL particle diameter plays a role that cannot be ignored. Hsu SH et al. indicated sdLDL-C is strongly associated with atherosclerotic risk markers, such as pre-diabetes, inflammation, thrombosis and hematological markers[30]. REN Limin et al. reported that the LDL particles in newly diagnosed type 2 diabetes were mainly sdLDL, which reached 55.8%, but only 3.3% in non-diabetics[31]. Our study also indicated that sdLDL-C level was closely related to the prevalence of PD and NT2D, especially the prevalence of NT2D in Q3 and Q4 groups achieves more than 2 times (Q3:11.0% vs. Q1:4.5%) and 3 times (Q4:14.5% vs. Q1:4.5%) of Q1, respectively. An association of LDL particle size with the cluster of risk factors that characterize the insulin resistance syndrome has been demonstrated[32]. A nested case-control study of 204 elderly men and women carried out in Finland clearly demonstrated that, subjects with a elevated level of sdLDL had more than two fold increased risk for developing T2D after a 3.5-year follow-up period, independent of age, gender, glucose tolerance and body mass index[33]. Rizvi et al. indicated that a measurement of sdLDL was worthwhile in women with Gestational diabetes mellitus(GDM). Multiple metabolic abnormalities including a

high sdLDL concentration were common in women with GDM, and revealed a greater risk for later occurrence of T2D and cardiovascular diseases (CVD)[34].

More than that, elevated levels of sdLDL-C could predict the risk for incident CHD and its severity even in individuals considered to be at a low risk for CVD based on their LDL-C levels[7]. Hsu H et al. assessed lipoprotein subfractions using novel assays in subjects with fasting normal, prediabetic, and diabetic Taiwanese men and women ($n = 2,049$), and suggested that direct LDL-C and sdLDL-C should be measured and optimized to reduce CVD risk in both prediabetic and diabetic populations[35]. Also there are studies showed that elevated sdLDL-C was a risk factor for Coronary Heart Disease (CHD) in normoglycemic individuals, those in the top sdLDL-C quartile showed higher risk of incident CHD (hazard ratio, 2.41; $P = 0.0037$), but this relationship was not observed in patients with impaired fasting glucose or T2D[36]. Some studies suggested that the increase of sdLDL-C indicated an increased risk of acute coronary syndrome(ACS), which were independent risk factors for ACS[37]. Shen H's results showed that sdLDL-C [1.278, 95% (1.019–1.598)], at final observation, was an independent risk of cardiovascular events, and a Kaplan-Meier survival analysis showed that patients with sdLDL-C > 38 mg/dl (logrank: 4.375, $P = 0.037$) were at increased risk for cardiovascular events[38]. After following up a total of 3,080 participants without prior cardiovascular disease and aged 40 years or older for 8 years, Higashioka M found that, as compared with subjects with sdLDL-C of < 32.9 mg/dL, the risk of coronary heart disease (CHD) almost doubled in subjects with sdLDL-C of ≥ 32.9 mg/dL, regardless of LDL-C levels. Therefore, a cut-off value of 35 mg/dL for sdLDL-C was proposed[39].

However, seldom studies have reported a clear target level for sdLDL-C in predicting the occurrence of pre-diabetes and/or newly discovered type 2 diabetes. Likely due to a lower affinity for the LDL-C receptor and thus has a longer circulation time, sdLDL-C has the characteristics of easier adhesion to the vascular wall, easier penetration into the arterial intima, slower plasma clearance, longer half-life, and more susceptible to qualitative modifications such as oxidation, dehydroxylation and glycosylation, so it deserves more attention than LDL-C[3]. Compared with direct measurement of LDL size, quantitative measurement of sdLDL-C levels could more accurately assess changes in the "quality" of LDL particles in patients with type 2 diabetes. In the past, there were few studies on sdLDL-C levels in patients with T2D due to methodological limitations. In our study, serum sdLDL-C and other lipid metabolism indicators were measured, and the logistic regression analysis showed that after adjusting for confounding variables (even after LDL-C was included in the model), the risk of PD and NT2D increased by 3.4% and 15.7% respectively. Our RCS curves also verified that with the increase of sdLDL-C, both the risk of PD and NT2D increased, indicating that sdLDL-C is a promising PD and NT2D risk factor independent of LDL-C. However, there was no nonlinear dose-response relationship between sdLDL-C level with pre-diabetes and newly detected type 2 diabetes in our study. Therefore, although there are many studies on the ability of sdLDL-C to predict cardiovascular events, whether it can be used as an indicator to screen out and intervene in people at high risk of diabetes and/or cardiovascular disease before diabetes is diagnosed, or to regulate blood lipid levels and prevent complications while controlling blood glucose during diabetes treatment, will be the focus of futrure research. We should enlarge the sample size, design prospective studies in different clinical groupings (such as different sdLDL-C level groupings, etc.), long-term follow-up studies, and intervention trials to further explore the specificity and sensitivity of sdLDL-C as well as the ideal target levels.

SdLDL-C showed different distributions by age and gender. Shen H et al.[40] measured sdLDL-C, glucose metabolism, lipid, blood pressure and carotid artery intima-media thickness in 183 native Chinese healthy subjects, and found that the sdLDL-C level in males was significantly higher than in females, and in both males and females there was an age effect on sdLDL-C. Based on a large representative sample from Japanese general population (5208 participants, 2397 men and 2811 women), Izumida T et al.[41] found that sdLDL-C differently distributed by age, gender and menopausal status. The sdLDL-C levels in men were higher than those in women until after the age of 75–79 years. The sdLDL-C levels in men increased with the age until peaked at 50–54 years and then decreased, while in women, relatively regular increasing trends until approximately 65 years, followed by a downward or pleated trend. The sdLDL-C levels were significantly different between premenopausal and postmenopausal women. In our study, there was age difference while no gender difference was observed among the four groups of sdLDL-C levels; and significant interaction of sdLDL-C levels was observed across age(≤ 55 or >55 years old) with PD, while across gender with NT2D. Different conclusions might be related to the different sample size, genetics, environmental factors and the selected population of each study. A subgroup-specific approach would be necessary to implement sdLDL-C for T2D and/or CVD prevention strategies, fully considering gender differences, age trends, menopausal status, and etc.

The mechanisms of dietary and gene on sdLDL-C are still being explored. It is essential to reduce TG levels and attenuate insulin resistance to decrease sdLDL particles[22]. This can be achieved effectively by improving lifestyle through diet, and etc. For example, dairy products and soy products are expected for a therapeutic diet while simple carbohydrates should be reduced or avoided, to effectively reduce visceral fat thus lowering sdLDL-C levels[42–44]. Hoogeveen RC et al.[7] performed genome-wide association study (GWAS) analyses and identified genetic variants in 8 loci associated with sdLDL-C levels. With the exception of the novel locus PCSK7, which was significantly associated with sdLDL-C and other lipid factors, all of these loci were in or close to genes previously found to be related to pathways involved in vascular inflammation and lipid metabolism. In this cross-sectional survey, data on dietary, lifestyle, and etc., as well as blood samples were collected, which is conducive to future researches on the mechanisms of dietary and genetic effects on sdLDL-C.

There were several limitations in our study. Firstly, this is a cross-sectional study, and thus we could describe associations, but no causal relationship could be drawn. The conclusions obtained need to be validated in prospective studies. Secondly, sdLDL-C is a dynamic change index, and there might be certain information bias when only one measurement was used. Thirdly, sdLDL-C are regulated through complex mechanisms, the confounding factors such as diet and genes were not considered, which might affect the authenticity of the

conclusion. Further researches, including prospective studies and long-term follow-up studies, as well as the analysis of the incorporation of dietary and genetics data, are strongly necessary to confirm and strengthen causal relationships. Lastly, the exclusion for patients who reported taking lipid-lowering and/or antidiabetic medications are reasonable to screen and describe the relationships of sdLDL-C and PD and NT2D. However, in real-world settings where many patients take these medications, our assessment is limited. Data regarding type and dose of medications should be collected and the associations of sdLDL-C and PD and NT2D in patients taking medications should be validated and improved in our further more in-depth and systematic researches. In addition, this study was conducted among residents of specific communities in Zhejiang Province, external studies in populations with different geographic, ethnic, or lifestyle characteristics, are needed to verify the validity and generalizability of our findings.

Our study has several strengths. It is a cross-sectional survey based on community adults aged 30–69 years, with a large sample size and good representation. Secondly, all biochemical indicators and questionnaire contents were measured and investigated by professionals in accordance with standard procedures after training, with good authenticity. Furthermore, excluding patients who had been diagnosed with T2D and those who took lipid-lowering drugs could exclude the influence of hypoglycemic and lipid-lowering drugs on the study results.

Conclusions

In our study, we found that with the increase of sdLDL-C level, the risk of PD and NT2D increased. The study supports that sdLDL-C is a promising risk factor for PD and NT2D independent of LDL-C. SdLDL-C combined with lipid monitoring is of great potensial value for early prevention, lipid-regulating drug treatment and prognosis of PD and NT2D.

Data availability

The data presented in this study are available on reasonable request from the corresponding author.

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Author contributions

Study concept and design: Q.H., M.L. and J.Z.; resources and supervision: R.H. and J.Z.; acquisition of data: L.W., Y.F. and M.L.; analysis and interpretation of data: Q.H. and X.C.; drafting of the manuscript: Q.H.; critical revision of the manuscript for important intellectual content: Q.H.and J.Z.

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Declarations

Competing interests

The authors declare no competing interests.

Disclosure
The study was approved by the Ethics Committee of Zhejiang Provincial Center for Disease Control and Prevention.

Informed consent
Written informed consent was obtained from all participants.

Additional information
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