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SMALL DENSE LOW-DENSITY LIPOPROTEIN CHOLESTEROL AND CENTRAL OBESITY ASSOCIATED WITH DIABETES MELLITUS AMONG INDONESIAN ADULTS

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ABSTRACT

Background: Small dense low-density lipoprotein (sdLDL-C) is an atherogenic lipoprotein. Increased sdLDL-C concentration was hypothesized to be associated with obesity and diabetes mellitus (DM). **Objectives**: The study aimed to determine the association between sdLDL-C, central obesity, and DM among Indonesian adults, controlled by personal and clinical parameters.

Materials and Methods: This study used secondary data from Basic Health Research 2013 of the Ministry of Health, which applied a cross-sectional study design. For this purpose, 30,548 subjects aged 19-79 were analyzed. The sdLDL-C was performed by using Sampson Formula derived from conventional lipid panels. As investigated by Sampson, the formula referred to cLDL-C (calculated LDL-C) and ElbLDL-C (estimated large buoyant LDL-C).

Results: There was a positive association between sdLDL-C and central obesity (OR: 3.94; 95% CI: 3.13-3.89), as well as sdLDL-C and DM status (OR: 1.98; 95% CI; 1.43-2.75) after adjusting the personal and clinical parameters.

Conclusion: This study demonstrated that the increment of sdLDL-C level and central obesity affected DM status in Indonesian adults. It implies that the sdLDL-C was a potential biomarker to assess the risk of DM.

Keywords: Central obesity, Diabetes mellitus, Hypertension, Indonesian adult, sdLDL-C

BACKGROUND

The prevalence of diabetes mellitus has risen worldwide over the last decade, and it is projected to increase further to 700 million by the year 2045. According to the national data, Indonesia has shown an increasing trend of diabetes mellitus. The number of 15 years and more with DM increased from 2007 to 2018, according to medical providers diagnosed [1], and it seems Indonesia has a higher prevalence than the Asia Pacific region [2]. DM is a complex disease, and dyslipidemia via insulin resistance is a critical causal factor in the development of many acute complications, including stroke, coronary artery disease (CAD), and renal destruction [3].

The numerous factors of DM are smoking, low physical activity, dietary pattern, age, gender, and dyslipidemia [4–10]. In addition, some studies considered the association of DM with education level, wealth [11], and place of living [12, 13]. Since diabetic dyslipidemia is highly prevalent in subjects with type 2 DM [14], the study of 140.557 subjects in Thailand showed that more than half of the subjects with T2DM had abnormalities in LDL-C, triglyceride (TG), and HDL-C [3]. The primary feature was slightly increased LDL-C, TG, and decreased HDL-C [15, 16]. Otherwise, LDL-C has a range in sizes and densities [17]. There is the scientific judgment that sdLDL-C as pattern B was more atherogenic since it has been characterized by small dense (< 25.5 nm) and lower affinity [18], they have a greater risk of endothelial penetration and causes of arterial stiffening [19, 20]. The current opinion states that insulin resistance in offspring was the leading cause of CVD events via vascular stiffening [21, 22]

The laboratory analysis method varies; the homogeneous assay and ultracentrifugation are commonly used [17, 18]. However, many researchers have developed the equation to calculate sdLDL-C derived from conventionally measured lipid panels [23, 24] according to the need for more technologies in the clinical setting, cost and time effectiveness being a consideration. The previous study on the association between sdLDL-C and CVD in Indonesia was investigated in children of 5-9 years [25], adults [22], DM subjects [26], and obese subjects [22] in a small sample size. Although sdLDL-C has been investigated in obese subjects, no studies have evaluated central obesity and DM status among Indonesian adults. Indonesia has enormous data on lipid profiles and potentially be used for calculating sdLDL-C concentration, with this data can mitigate a potential risk factor of elevated sdLDL-C, central obesity, and DM status in each characteristic. The current

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study aimed to determine the association between sdLDL-C, central obesity, and DM status by controlling personal and clinical parameters.

MATERIALS AND METHODS

Design and Sampling

This study analyzed the secondary data using a cross-sectional study of Basic Health Research 2013 (Riset Kesehatan Dasar 2013) collected by the National Institute of Health Research Development (NIHRD), Ministry of Health, Indonesia. The protocol and study method of Basic Health Research has been published in detail elsewhere [1]. The study subject was selected by multistage stratified sampling (fig.1). The final subject was drawn from a 1000-block census of province estimation which was nationally representative. The potentially eligible subject was 34,007, and the advanced analysis was completed from February to July 2022.

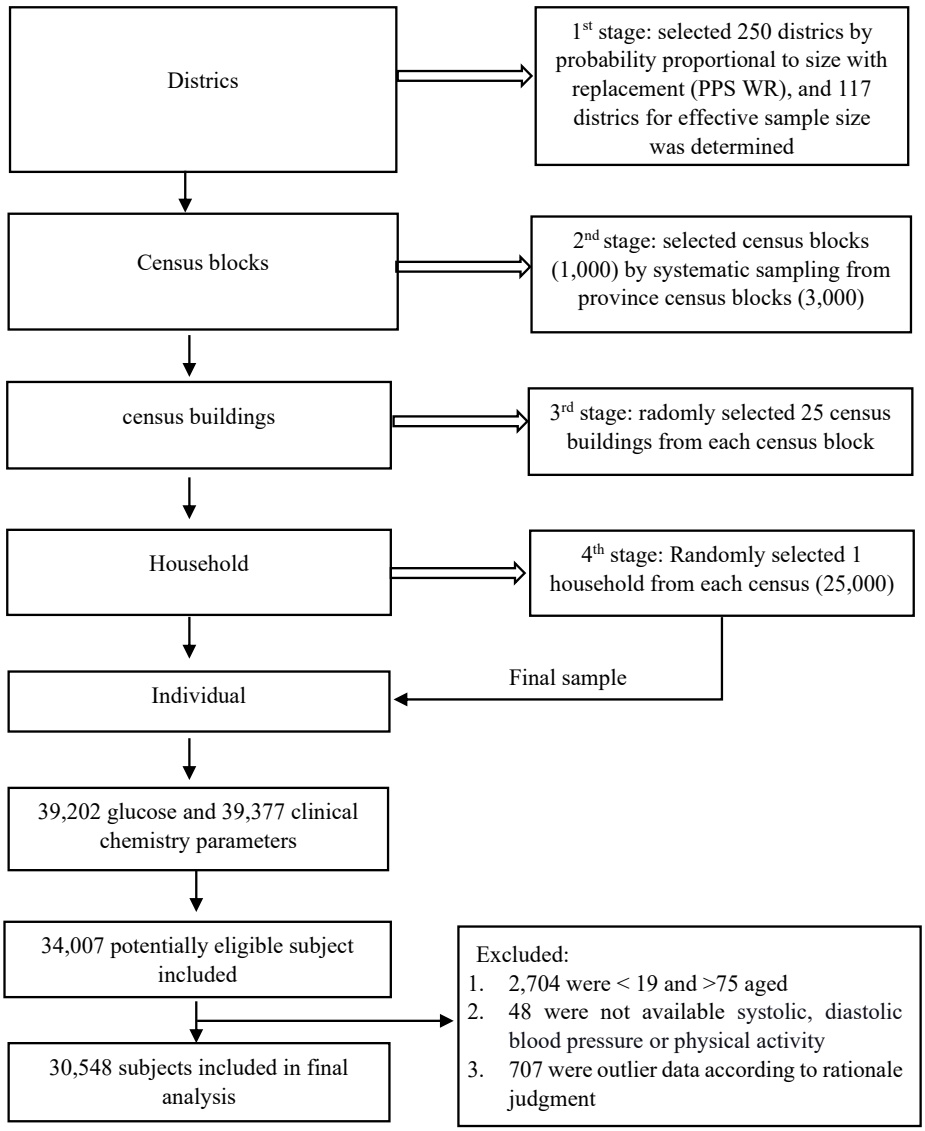

Fig 1. Flow diagram of selection study subjects. Modified from The Ministry of Health[1].

Data Processing

The subjects were Indonesian, aged 19-79 years, and well-trained laboratory analysts took subjects assessed in clinical biochemistry. Missing data on blood pressure and physical activity, and TG concentration was 800 mg/dL above, excluded from the study. The number of subjects was 34,007, and 30,548 were included in the analysis after applying the exclusion criteria. Each parameter of plasma glucose was carried out to examine the correlational analysis of personal and clinical parameters with plasma glucose. The number of subjects with glucose parameters was 2.201, 23.635, and 6.913 for 2 hours, fasting and random plasma glucose, respectively.

Sociodemographic Parameters

Direct interviews with a questionnaire were used to collect sociodemographic parameters, including age, gender, place of living, education attainment, occupation, and economic status. This study used a newly redefined age group and the possible link between disease in human lifespan by Giefman et al. [2]; the age study subjects were stratified into four categories;19-33 years, 34-48 years, 49-64 years, and ≥ 65 years. Education attainment is classified into three categories: 'primary' (less than senior high school), 'secondary' (senior high school), and 'college' (diploma or above). Five categories of occupation are used; farmer/fisher/laborer, professional worker, self-employed, other, and unemployment. Economic status was assessed by Principal Component Analysis (PCA), resulting in quintiles from lowest to highest. The correlational polychoric was used to generate the PCA matrix. Only the variable with more than 0.3 correlational value and more than 0.5 proportion explained can be used as a predictor economic status variable [1, 3]. There were 12 selection variables, including water supply, cooking fuel type, toilet usage, toilet type, disposal habits, lighting type, and ownership of the motorcycle, TV, water heater, 12 kg gas cylinder, refrigerator, and car.

Smoking Habit, Physical Activity, and Dietary Fruits and Vegetables

Smoking status was classified as non-smoker, former smoker, and smoker. A modified GPAQ (Global Physical Activity questionnaire) was used to assess vigorous and moderate physical activity and sedentary behavior. Physical activity level was defined by calculating METs per minute for each dimension by multiplying 4.0 and 8.0 METs for vigorous and moderate over a week period [2]. Calculated physical activity levels on Mets/minute/week were then classified as sedentary, low, moderate, and active. Sedentary time was defined as not having moderate or intense physical activity on any day of the previous week. In comparison, high physical activity was defined as taking a score ≥3000 METs-minute/week. Moderate physical activity was taking a score of 2999-600 METs-minute/week, and low physical activity failed to meet any criteria above. Dietary fruits and vegetables were collected by a simple questionnaire that asked consumption frequency per week and the serving size per day, thus were categorized into: never, <3 portions per day, 3-4 per day, and ≥5 per day.

Clinical Parameters

The sdLDL-C was defined following the Sampson equation: elbLDL-C: 1.43xLDL-C – (0.14x(ln(TG)xLDLC))- 8,99, and the sdLDL-C: LDL C–elbLDL-C that refers to current calculated LDL-C (cLDL-C) equation which proposed by Sampson [2]. A new equation of cLDL-C seems more accurate and possibly be used in patients with low LDL-C levels and hypertriglyceridemia (TG levels, ≤800 mg/dL) than the previous equation [3]. The body mass index based on the Quetelet index (kg/m^2) was defined into three criteria [4]; normal (≥25.0), overweight (25.1-27.00), and obesity (≥27.1), and central obesity was defined as a waist circumference of ≥ 90 and ≥80 cm [5], for man and women respectively.

Lipid parameters were classified according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel [6]. The abnormal values were defined following lipid levels; ≥200 mg/dl (TC), 100 mg/dl (LDL-C), and 150 gr/dl (TG), while HDL-C was <40 mg/ dl and <50 mg/dl for men and women respectively. High levels of creatinine were referred to in the previous study (≥1.2 and ≥1.1 mg/dl for men and women, respectively) [7]. The blood pressure was defined according to global hypertension practice guidelines (systolic≥ 140 mmHg or diastolic ≥90 mmHg) [8]. DM was defined according to plasma glucose measurement referring to ADA classification. The cut-off was fasting plasma glucose ≥126 mg/dL or 2 hours (postprandial) plasma glucose ≥200 mg/dl or random plasma glucose ≥200 mg/dL with the classic symptom [9] or refer to the diagnosis of medical providers.

Statistical Analysis

Data were analyzed using SPSS 25 version, summary statistic results of subject characteristics stratified by quintile of sdLDL-C. Data were expressed as a percentage for categorical variables and mean±standard deviation for continuous variables. Cut-off sdLDL-C were defined as Q1 (≤ 24.86 mg/dl), Q2 (24.87-31.06 mg/dl), Q3 (30.07-37.74 mg/dl), Q4 (37.75-46.11 mg/dl), and Q5 (≥ 46.12 mg/dl). Quintile 1 was chosen as a reference and considered the lowest-risk group for the outcome. Kruskal-Wallis tests were performed to analyze variables across quintiles for continuous variables. Single binary logistic regression analyses were used to attain the association between each variable and DM with 95% CI and multinomial logistic regression for each variable and sdLDL-C across quintiles. The strength of the association was expressed by adjusted odds ratios (aOR) and 95% CI. $p<0.05$ was recognized as statistically significant.

RESULTS

Characteristics of the Study Subjects According to Quintile sdLDL-C

The baseline personal and clinical characteristics of the study subjects are summarized in Table 1. The average age was 42.59 ± 15.78 years old. More than half of the subjects resided in rural areas, there was a similar proportion of men and women, nearly three-quarters had low education (73,0; 95% CI: 71,7-74,3), and more than three-quarters (75.2; 95% CI: 71.2-73.8) were classified as active. The percentage of participants who consumed the recommended amounts of fruits and vegetables was relatively low. Although LDL-C and 2h-PG results tended to be higher than normal, the overall mean clinical parameters tended to classify within normal values.

Table 1. Baseline characteristic of the study subjects (n:30,548)

Variabel	% (95% CI)[a]
Age (years)	42.59±15.78
Gender	
Men	49.9 (48.7-51.1)
Women	50.1 (48.9-51.3)
Place of living	
Urban	43.7 (43.1-44.4)
Rural	56.3 (55.6-56.9)
Education attainment	
Primary	73.0 (71.7-74.3)
Secondary	22.0 (21.0-23.1)
Collage	4.9 (4.4-5.5)
Occupation	
Farmer/fisher/laborer	33.5 (32.2-34.7)
Professional worker	10.9 (10.2-11.8)
Self-employed	13.7 (13.0-14.5)
Others	3,9 (3.5-4.3)
Unemployment	38.0 (37.0-39.0)
Economic status	
Lowest	13.8 (12.6-15.2)
Low	20.5 (19.3-21.8)
Middle	24.5 (23.3-25.8)
High	24.2 (23.0-25.5)
Highest	16.8 (15.6-18.2)
Smoking Habit	
Never	61.7 (61.0-62.5)
Former	5.0 (4.7-5.4)
Current	33.2 (32.5-34.0
Physical activity	
Sedentary	7.4 (6.6-8.2)
Low	3.3 (2.9-3.6)
Moderate	16.9 (16.0-17.8)
Active	75.2 (71.2-73.8)
Dietary Fruits and Vegetable	
Never	0.9 (0.7-1.1)
< 3 (portion/day)	80.0 (78.8-81.2)
3-4 (portion/day)	16.1 (15.5-17.6)
≥ 5 (portion/day)	2.6 (2.3-3.0)
BMI (kg/m^2)	23.1±4.2
Waist circumference (cm)	78.5±11.0
TC (mg/dl)	188.1±39.8
HDL-C (mg/dL)	41.7±15.0
LDL-C (mg/dL)	126.10±35.27
TG (mg/dl)	123.4±74.8
sdLDL-C (mg/dL)	35.9±13.0
2h-FG (n=2.201)	142.3±51.7
FPG (n=23.635)	104.4±30.2

Variabel	% (95% CI)[a]
RPG (n=6.913)	114.7±41.3
Creatinine (mg/dL)	0.81±0.25
Sistolic (mmHg)	128.2±21.3
Diastolic (mmHg)	82.4±11.9

Data illustrated the weighted percentages and 95% CI for the categorical variable and mean±SD for the continuous variable.
BMI: Body Mass Index; TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TG: Triglycerides; 2h-FG: 2-Hour Plasma Glucose; FPG: Fasting Plasma Glucose; RDP: Random Plasma Glucose; sdLDL-C: Small Dense LDL-C According to Sampson Equation.

The distribution of personal and clinical risk factors of DM according to the quintile sdLDL-C are summarized in Table 2. The proportion of quintile 5 sdLDL-C (≥ 46.12) was higher in 49-64 aged and higher in men than women and urban than rural populations. The study also showed that quintile 5 was highly prevalent in college education level, self-employed, and subjects with the highest quintile economic status. In addition, the proportion of sdLDL-C levels increased gradually across the quintile from the subject who smoked and never consumed fruits and vegetables. In contrast, sdLDL-C levels decreased gradually in the physically active subjects.

Table 2. Percentages of Subjects for Each Personal Risk Factor of DM Status According to sdLDL-C Quintile

Variable	Quintile sdLDL-C (95% CI)				
	Q1	Q 2	Q3	Q 4	Q5
Age (years)					
19-33	31.7 (30.3-	24.7 (23.4-	19.5 (18.4-	14.3 (13.3-	
34-48	33.1)	26.0)	20.7)	15.4)	9.8 (8.9-10.7)
49-64	16.5 (15.6-	20.3 (19.4-	20.9 (20.0-	21.4 (20.5-	20.8 (19.8-
≥ 65	17.6)	21.2)	21.9)	22.4)	21.8)
	11.0 (10.1-	15.3 (14.3-	20.1 (18.8-	23.7 (22.5-	29.9 (28.5-
	12.1)	16.4)	21.3)	25.0)	31.3)
	13.4 (11.7-	19.4 (17.5-	21.8 (19.9-	21.6 (19.6-	23.9 (21.7-
	15.2)	21.4)	23.8)	23.7)	26.2)
Gender					
Men	16.6 (15.7-	20.2 (19.3-	21.0 (20.0-	21.4 (20.4-	20.9 (19.9-
Women	17.6)	21.1)	21.9)	22.3)	21.9)
	22.9 (21.9-	20.9 (20.1-	19.8 (19.1-	18.2 (17.4-	18.2 (17.4-
	23.9)	21.7)	20.6)	18.9)	19.0)
Place of living					
Urban	19.9 (19.6-	19.6 (18.7-	19.6 (18.8-	19.3 (18.3-	21.5 (20.4-
Rural	19.6)	20.6)	20.5)	20.3)	22.7)
	20.4 (21.5-	21.5 (20.7-	21.0 (20.2-	19.8 (19.1-	17.2 (16.3-
	21.0)	22.4)	21.9)	20.6)	18.1)
Education attainment					
Primary	19.5 (18.6-	20.7 (20.0-	20.8 (20.2-	20.2 (19.5-	18.7 (17.9-
Secondary	20.5)	21.4)	21.6)	20.9)	19.5)
Collage	22.7 (21.2-	20.9 (19.5-	18.8 (17.5-	17.9 (16.6-	19.7 (18.4-
	24.3)	22.4)	20.0)	19.2)	21.2)
	18.3 (15.9-	17.3 (14.7-	19.6 (17.2-	17.9 (15.7-	26.8 (23.8-
	21.1)	20.3)	22.2)	20.4)	30.1)
Occupation	18.5 (17.4-	22.0 (21.0-	21.7 (20.7-	20.6 (19.6-	17.1 (16.1-
Farmer/fisher/laborer	19.7)	23.1)	22.7)	21.7)	18.1)
Professional worker	19.9 (18.0-	18.2 (16.5-	19.4 (17.5-	20.3 (18.4-	22.2 (20.4-
Self-employed	22.0)	20.1)	21.4)	22.4)	24.0)
Others	16.4 (14.9-	18.5 (17.0-	20.4 (18.9-	20.5 (18.9-	24.2 (22.6-
Unemployment	18.1)	20.1)	21.9)	22.1)	26.0)
	21.6 (18.8-	18.1 (15.5-	19.6 (16.5-	21.4 (18.6-	19.3 (16.8-
	24.7)	21.0)	23.0)	24.6)	22.1)
	22.9 (21.7-	21.0 (20.1-	19.5 (18.5-	17.9 (16.9-	18.8 (17.8-
	24.1)	22.0)	20.5)	18.8)	19.8)
Economic status					
Lowest	22.2 (20.3-24.2)	22.0 (20.6-23.5)	21.0 (19.6-22.4)	19.7 (18.1-21.4)	15.1 (13.7-16.6)
Low	21.5 (19.9-23.1)	21.7 (20.5-22.9)	22.1 (20.9-23.4)	18.6 (17.4-19.9)	16.1 (14.9-17.3)
Middle	20.8 (19.4-22.3)	21.8 (20.6-23.1)	20.2 (19.1-21.4)	19.0 (17.9-20.2)	18.1 (17.0-19.2)

Variable	Quintile sdLDL-C (95% CI)				
	Q1	Q 2	Q3	Q 4	Q5
High	19.4 (18.0-20.9)	19.3 (18.2-20.4)	20.0 (18.8-21.3)	20.1 (18.8-21.4)	21.2 (19.9-22.6)
Highest	17.0 (15.7-18.4)	18.2 (16.8-19.7)	18.2 (16.9-19.5)	20.6 (19.2-22.0)	26.0 (24.3-27.8)
Smoking Habit					
Never	22.6 (21.6-23.5)	21.0 (20.2-21.7)	19.8 (19.1-20.6)	21.7 (19.8-19.1)	20.6 (18.4-17.7)
Former	14.8 (12.4-17.6)	19.5 (17.1-22.1)	20.3 (17.8-23.0)	22.1 (20.3-17.8)	23.0 (20.9-18.5)
Current	16.5 (15.5-17.6)	20.1 (19.0-21.2)	21.3 (20.2-22.4)	21.2 (21.3-20.2)	22.4 (21.5-20.5)
Physical activity					
Sedentary	18.8 (16.1-21.9)	20.5 (18.1-23.1)	18.4 (16.2-20.8)	20.5 (18.2-23.1)	21.8 (19.2-24.7)
Low	20.3 (17.1-24.0)	17.3 (14.6-20.5)	18.3 (15.2-21.8)	19.2 (16.4-22.4)	24.8 (21.5-28.5)
Moderate	20.5 (19.0-22.2)	19.3 (17.8-20.8)	19.9 (18.5-21.5)	19.1 (17.8-20.5)	21.2 (19.7-22.7)
Active	20.2 (19.4-21.1)	21.1 (20.4-21.8)	20.7 (20.0-21.4)	19.6 (18.8-20.4)	18.4 (17.7-19.2)
Dietary Fruits and Vegetable					
Never	18.6 (13.0-25.7)	18.7 (13.1-26.0)	19.9 (14.4-26.9)	18.1 (12.7-25.2)	24.7 (19.6-30.5)
< 3 (portion/day)	20.4 (19.5-21.3)	20.5 (19.9-21.2)	20.2 (19.5-20.9)	19.7 (18.9-20.4)	19.2 (18.4-19.9)
3-4 (portion/day)	19.5 (18.0-21.1)	21.2 (19.8-22.8)	20.8 (19.4-22.2)	19.0 (17.6-20.5)	19.4 (17.9-21.0)
≥ 5 (portion/day)	16.9 (13.7-20.6)	18.8 (15.3-22.9)	21.3 (18.0-25.0)	20.3 (17.1-23.8)	22.8 (19.0-27.0)

Data ilustrated the weighted percentages and 95% CI. sdLDL-C value defined as Q1 (≤ 24.86 mg/dl), Q2 (24.87-31.06 mg/dl), Q3 (30.07-37.74 mg/dl), Q4 (37.75-46.11 mg/dl) and Q5 (≥ 46.12 mg/dl).

The Kruskal-Wallis test was used to assess the mean in different clinical parameters according to quintile sdLDL-C are shown in Table 3. As expected, the mean BMI, waist circumference, TC, LDL-C, TG, and 2h-PG, FPG, RP, creatinine, and blood pressure were significantly increased, while HDL-C declined across the quintiles.

Table 3. Mean of Clinical Risk Factors of DM Status According to sdLDL-C Quintiles

Variable	Quintile sdLDL-C (mean±SD)					*p-value*
	Q1 n: 6,105	Q 2 n: 6,109	Q3 n: 6,105	Q 4 n: 6,113	Q5 n: 6,116	
BMI (kg/m^2)	21.6±3.6	22.3±3.9	23.1±4.0	23.7±4.2	24.7±4.2	**<0.001**
Waist circumference (cm)	74.2±9.3	76.1±10.1	78.0±10.6	80.2±11.0	83.6±11.2	**<0.001**
TC	147.2±26.1	168.7±22.1	184.6±22.1	201.8±21.9	238.1±32.1	**<0.001**
HDL-C	52.6±14.8	50.7±11.8	49.0±11.6	46.9±11.3	44.3±10.7	**<0.001**
LDL-C	89.7±20.7	109.0±18.4	123.6±19.8	138.4±20.9	169.1±31.1	**<0.001**
TG	64.3±28.8	89.5±33.8	112.3±41.8	143.4±58.0	207.2±93.1	**<0.001**
2h-FG (n=2.201)	132.4±38.7	135.4±43.6	140.3±45.7	142.9±51.0	160.9±.69.8	**<0.001**
FPG (n=23.635)	97.8±16.1	100.0±19.2	102.4±23.3	105.3±30.5	116.6±47.8	**<0.001**
RPG (n=6.913)	107.1±31.2	110.0±29.3	111.2±30.3	114.6±39.0	128.3±61.0	**<0.001**
Creatinine (mg/dl)	0.75±0.23	0.79±0.24	0.81±0.23	0.83±0.24	0.86±0.30	**<0.001**
Sistolic (mmHg)	121.6±18.5	125.1±20.1	128.0±21.1	130.8±21.4	135.4±22.7	**<0.001**
Diastolic (mmHg)	79.1±10.7	80.7±11.20	82.1±11.5	83.8±12.0	86.1±12.5	**<0.001**

BMI: Body Mass Index; TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TG: Triglycerides; 2h-FG: 2-Hour Plasma Glucose; FPG: Fasting Plasma Glucose; RDP: Random Plasma Glucose; sdLDL-C: Small Dense LDL-C According to Sampson Equation.
Kruskal-Wallis test for continuous values
The bold number was statistically significant.

Correlational Analysis Between Personal and Clinical Parameters with Plasma Glucose

The coefficient correlation (r) is shown in Table 4. Spearman analysis showed that sdLDL-C was independently correlated with plasma glucose parameters, and the highest r value was found in the FPG parameter (r=0.211). It was also found that BMI, waist circumference, TC, LDL-C, TG, creatinine, systolic, and diastolic blood pressure were statistically positively correlated with plasma glucose. In contrast to METs-minute/week, dietary fruits and vegetables and HDL-C tended to be negatively associated with plasma glucose.

Table 4. The r and p Values of Personal and Clinical Parameters with Plasma Glucose Correlation

Variables	2h-PG (n=2,201)		FPG (n= 23,635)		RPG (n=6,913)	
	r	p-value	r	p-value	r	p-value
Age (years)	0.199	**<0.001**	0.254	**<0.001**	0.264	**<0.001**
Mets-minute/week	-0.077	**<0.001**	0.001	0.908	-0.008	0.525

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Variables	2h-PG (n=2,201)		FPG (n= 23,635)		RPG (n=6,913)	
	r	p-value	r	p-value	r	p-value
Sedentary time	0.022	**<0.001**	-0.006	0.353	0.007	0.544
Dietary Fruits and Vegetable	0.017	**0.012**	-0.002	0.718	-0.002	0.842
BMI (kg/m^2)	0.103	**<0.001**	0.058	**<0.001**	0.080	**<0.001**
Waist circumference (cm)	0.124	**<0.001**	0.100	**<0.001**	0.113	**<0.001**
TC	0.145	**<0.001**	0.144	**<0.001**	0.115	**<0.001**
HDL-C	-0.018	**0.008**	-0.085	**<0.001**	-0.103	**<0.001**
LDL-C	0.140	**<0.001**	0.141	**<0.001**	0.105	**<0.001**
TG	0.116	**<0.001**	0.213	**<0.001**	0.188	**<0.001**
Creatinine (mg/dl)	-0.083	**<0.001**	0.043	**<0.001**	0.175	**<0.001**
Systolic (mmHg)	0.179	**<0.001**	0.201	**<0.001**	0.034	**0.004**
Diastolic (mmHg)	0.150	**<0.001**	0.112	**<0.001**	0.204	**<0.001**
sdLDL-C	0.153	**<0.001**	0.211	**<0.001**	0.112	**<0.001**

BMI: Body Mass Index; TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TG: Triglycerides; 2h-FG: 2-Hour Plasma Glucose; FPG: Fasting Plasma Glucose; RDP: Random Plasma Glucose; sdLDL-C: Small Dense LDL-C According to Sampson Equation
The bold number was statistically significant

Correlational Analysis Between sdLDL-C, Central Obesity, and DM Status

The OR and 95% CI of personal and clinical parameters among the sdLDL-C quintiles are shown in Table 5. Clustering of age demonstrated a positive association between sdLDL-C and age. In comparison, in Q5 vs. Q1, the 49-64 years group owned the highest risk of sdLDL-C (OR: 8.89; 95% CI: 7.69-10.28), while gender consideration demonstrated that women were found to have about 35% lower risk increasing of sdLDL-C level than man (OR: 0.65; 95% CI: 0.59-0.71). Similarly, place of living showed that subjects living in rural areas found about a 23% decrease in sdLDL-C (OR: 0.77; 95% CI: 0.68-0.88). Given education attainment, subjects who completed a diploma or above tended to increase sdLDL-C (OR: 1.59; 95% CI: 1.27-1.99), as seen in the professional and self-employed occupation group (OR: 1.22; 95% CI: 1.03-1.44; OR:1.62; 95% CI:39-1.89, respectively). The study also showed that the highest economic status group increased the 2.29-time risk of elevated sdLDL-C (OR: 2.29; 95% CI: 1.86-2.76).

The study identified smoking habits, physical activity, and dietary fruits and vegetables as risk factors related to sdLDL-C. The study showed that former and current smokers have an increased risk of elevated sdLDL-C (OR: 1.95; 95% CI: 1.54-2.46; OR: 1.51: 95% CI: 1.37-1.66, respectively) contrary to physical activity reduced by 22 % (OR: 0.78; 95% CI: 0.62-0.98) the risk of elevated sdLDL-C. The results showed no association between sdLDL-C and dietary fruits and vegetables. A cross quintile of sdLDL-C obesity subjects was founded to increase the risk of elevated sdLDL-C as seen in central obesity (OR: 5.09; 95% CI: 4.40-5.90; OR: 3.49; 95% CI: 3.13-3.89, respectively). The study also found the increase of creatinine and blood pressure strongly associated with elevated sdLDL-C (OR: 4.46: 95% CI: 3.40-5.87; OR: 3.31; 95% CI: 2.96-3.69, respectively).

Table 5. The OR and 95% CI Values of Personal and Clinical Parameters According to sdLDL-C Quintiles

Variable	Quintile sdLDL-C (mean±SD)				
	Q1	Q 2	Q3	Q 4	Q5
Age (years)					
19-33	ref	ref	ref	ref	ref
34-48		**1.56 (1.41-1.74)**	**2.04 (1.83-2.28)**	**2.89 (2.59-3.23)**	**4.00 (3.51-4.56)**
49-64		**1.82 (1.59-2.08)**	**2.99 (2.60-3.44)**	**4.81 (4.18-5.53)**	**8.89 (7.69-10.28)**
≥ 65		**1.94 (1.60-2.58)**	**2.56 (2.11-3.11)**	**3.69 (3.06-4.45)**	**5.75 (4.65-7.10)**
Gender					
Men	ref	ref	ref	ref	ref
Women		**0.77 (0.71-0.85)**	**0.69 (0.62-0.76)**	**0.64 (0.58-0.70)**	**0.65 (0.59-0.71)**
Place of living					
Urban	ref	ref	ref	ref	ref
Rural		1.05 (0.95-1.16)	1.05 (0.94-1.17)	0.97 (0.87-1.09)	**0.77 (0.68-0.88)**
Education attainment					
Primary		ref	ref	ref	ref
Secondary	ref	**0.85 (0.75-0.97)**	**0.74 (0.66-0.84)**	**0.87 (0.69-0.88)**	0.90 (0.79-1.03)
Collage		0.90 (0.72-1.14)	1.01 (0.82-1.24)	0.97 (0.78-1.20)	**1.59 (1.27-1.99)**

Variable	Quintile sdLDL-C (mean±SD)				
	Q1	Q 2	Q3	Q 4	Q5
Occupation					
Farmer/fisher/laborer	ref	ref	ref	ref	ref
Professional worker		**0.75 (0.64-0.88)**	0.85 (0.71-1.01)	0.96 (0.80-1.15)	**1.22 (1.03-1.44)**
Self-employed		0.95 (0.81-1.11)	1.08 (0.93-1.26)	1.14 (0.98-1.32)	**1.62 (1.39-1.89)**
Others		**0.73 (0.58-0.92)**	**0.73 (0.56-0.95)**	0.93 (0.73-1.18)	0.99 (0.73-1.18)
Unemployment		**0.77 (0.69-0.85)**	**0.74 (0.66-0.82)**	**0.72 (0.64-0.81)**	0.91 (0.81-1.02)
Economic status					
Lowest	ref	ref	ref	ref	ref
Low		1.01 (0.88-1.16)	1.05 (0.89-1.23)	0.97 (0.81-1.17)	1.07 (0.89-1.27)
Middle		1.01 (0.89-1.27)	0.99 (0.85-1.17)	1.01 (0.84-1.22)	**1.24 (1.04-1.49)**
High		0.93 (0.81-1.08)	1.07 (0.90-1.27)	1.16 (0.97-1.39)	**1.56 (1.29-1.89)**
Highest		1.04 (0.89-1.22)	1.16 (0.89-1.22)	**1.36 (1.13-1.69)**	**2.29 (1.86-2.76)**
Smoking habit					
Never	ref	ref	ref	ref	ref
Former		**1.33 (1.04-1.71)**	**1.51 (1.19-1.91)**	**1.58 (1.26-1.97)**	**1.95 (1.54-2.46)**
Current		**1.29 (1.17-1.42)**	**1.47 (1.33-1.63)**	**1.55 (1.40-1.72)**	**1.51 (1.37-1.66)**
Physical activity					
Sedentary	ref	ref	ref	ref	**ref**
Low		0.87 (0.63-1.21)	0.88 (0.62-1.25)	0.96 (0.70-1.32)	1.08 (0.78-1.50)
Moderate		0.93 (0.73-1.17)	1.02 (0.79-1.32)	0.91 (0.72-1.14)	0.89 (0.69-1.16)
Active		1.00 (0.81-1.23)	1.06 (0.85-1.32)	0.93 (0.76-1.13)	**0.78 (0.62-0.98)**
Dietary Fruits and Vegetable					
never	ref	ref	ref	ref	ref
< 3 (portion/day)		0.91 (0.53-1.55)	0.97 (0.57-1.65)	0.99(0.55-1.80)	0.68(0.44-1.04)
3-4 (portion/day)		0.97 (0.56-1.67)	1.04 (0.61-1.78)	1.00(0.55-1.81)	0.72(0.46-1.12)
≥ 5 (portion/day)		1.06 (0.57-1.96)	1.14 (0.63-2.06)	1.21(0.64-2.29)	0.96(0.57-1.62)
General obesity					
Normal	ref	ref	ref	ref	ref
Overweight		1.26 (1.06-1.50)	1.79 (1.53-2.09)	2.06 (1.76-2.42)	3.16 (2.72-3.66)
Obesity		1.65 (1.42-1.93)	2.23 (1.91-2.60)	3.16 (2.74-3.65)	5.09 (4.40-5.90)
Central Obesity					
Normal	ref	ref	ref	ref	ref
Obesity		1.39 (1.24-1.56)	1.68 (1.51-1.88)	2.29 (2.05-2.55)	3.49 (3.13-3.89)
Creatinine Level					
Normal	ref	ref	ref	ref	ref
High		1.55 (1.16-2.06)	1.88 (1.40-2.53)	2.63 (2.01-3.45)	4.46 (3.40-5.87)
Blood pressure					
Normal	ref	ref	ref	ref	ref
Hypertension		1.37 (1.22-1.53)	1.72 (1.54-1.93)	2.33 (2.08-2.60)	3.31 (2.96-3.69)

*The OR illustrated the weight analysis
The bold number was statistically significant
ref was reference values

The association between sdLDL-C, central obesity, and DM status is shown in table 5. Increasing age was associated with an increased risk of DM status. In crude analysis, the study found that sex and DM were statistically significant (OR: 1.37; 95% CI: 1.25-1.50) for women, and DM was not significant comparing rural vs. urban. The study found that professional workers had a lower risk of DM status (OR: 0.77; 95% CI: 0.63-0.94). In contrast, other and unemployed groups had a higher risk of DM status than Farmer/fisher/laborer (OR: 1.41; 95% CI: 1.11-1.78; OR: 1.25; 95% CI: 1.11-1.41, respectively). We did not find the risk of economic status and DM status.

The analysis showed a higher risk of DM status for a former smoker (OR: 1.24; 95% CI: 1.03-1.50). In contrast, current smokers had a lower risk of DM status (OR. 0.68: 95% CI. 0.62-0.76) vs. the non-smoker group. This study showed the inverse association between physical activity and DM. Moderate and vigorous activity decreased 22% and 34% risk of DM status (OR 0.78: 95% CI. 0.64-0.95; OR. 0.66: 95% CI. 0.55-0.80, respectively) compared to the sedentary group, while there was not statistically significant difference between dietary fruits and vegetables with DM status.

These analyses demonstrated a significant association of sdLDL-C across quintile, as well as obesity and central obesity with DM status (OR: 3.92: 95% CI; 3.34-4.36; OR 1.96; 95% CI; 1.72-2.21; OR: 2.02; 95% CI: 1.83-2.22. respectively). In addition, the increment of TC, LDL-C, and TG levels increased the risk of DM 2.12, 1.89, and 2.02 times, respectively. Similar trends were also found in creatinine and hypertension. Subjects with a high level of creatinine and hypertension were more likely than the normal group (OR: 1.91; 95% CI: 1.58-2.31; OR: 2.46; 95% CI: 2.23-2.71. respectively). However, this analysis did not find any significant association with HDL-C.

Table 6. Crude and Adjusted OR 95% CI Values of Personal and Clinical Parameters with DM Status Correlation

Variabel	OR (95% CI)[a]	
	Crude	adjusted
Age (years)		
19-33	ref	ref
34-48	**2.94 (2.50-3.45)**	**2,40 (2,02-2,86)**
49-64	**5.93 (5.02-7.00)**	**4,25 (3.52-5.13)**
≥ 65	**7.42 (6.13-8.98)**	**5.45 (4.40-6.76)**
Gender		
Men	ref	ref
Women	**1.37 (1.25-1.50)**	1.03 (0.86-1.24)
Place of living		
Urban	ref	
Rural	1.08 (0.96-1.22)	-
Education attainment		
Primary	ref	ref
Secondary	**0.60 (0.53-0.69)**	**0.83 (0.72-0.96)**
Collage	**0.75 (0.58-0.96)**	0.78 (0.60-1.02)
Occupation		
Farmer/fisher/laborer	ref	ref
Professional worker	0.77 (0.63-0.94)	0.88 (0.75-1.02)
Self-employed	1.06 (0.90-1.25)	0.88 (0.71-1.11)
Others	**1.41 (1.11-1.78)**	0.90 (0.76-1.07)
Unemployment	**1.25 (1.11-1.41)**	1.27 (0.99-1.61)
Economic status		
Lowest	ref	
Low	0.84 (0.71-0.99)	-
Middle	0.86 (0.73-1.02)	
High	0.96 (0.80-1.14)	
Highest	0.98 (0.81-1.18)	
Smoking habit		
Never	ref	ref
Former	**1.24 (1.03-1.50)**	1.00 (0.78-1.27)
Current	**0.68 (0.62-0.76)**	**0.78 (0.66-0.93)**
Physical activity		
Sedentary	**ref**	
Low	1.01 (0.75-1.35)	1.10 (0.82-1.48)
Moderate	**0.78 (0.64-0.95)**	0.84 (0.69-1.03)
Active	**0.66 (0.55-0.80)**	0.83 (0.69-1.00)
Active		
Dietary Fruits and Vegetable (portion/day)		
Never	ref	
< 3	0.74 (0.48-1.13)	-
3-4	0.83 (0.54-1.28)	
≥ 5	0.79 (0.48-1.31)	
General obesity		
Normal	ref	
Overweight	**1.47 (1.27-1.69)**	1.07 (0.91-1.26)
Obesity	**1.96 (1.74-2.21**)	**1.28 (1.10-1.50)**
Central Obesity	ref	ref
Normal	**2.02 (1.83-2.22)**	**1.34 (1.17-1.53)**

Variabel	OR (95% CI)[a]	
	Crude	adjusted
Obesity		
High TC		
Normal	ref	ref
High	**2.12 (1.93-2.33)**	0.97 (0.84-1.12)
Low HDL-C		
Normal	ref	
Low	0.96 (0.87-1.05)	-
High LDL-C		
Normal	ref	ref
High	**1.89 (1.67-2.14)**	0.97 (0.81-1.16)
High TG		
Normal	ref	ref
High	**2.02 (1.84-2.23)**	**1.21 (1.05-1.40)**
Quintile sdLDL-C		
Q1	ref	ref
Q2	**1.26 (1.05-1.51)**	1.05 (0.85-1.29)
Q3	**1.69 (1.41-2.02)**	1.28 (1.01-1.62)
Q4	**2.02 (1.69-2.42)**	1.26 (0.96-1.66)
Q5	**3.92 (3.32-4.63)**	**1.98 (1.43-2.75)**
Creatinine Level		
Normal	ref	ref
High	**1.91 (1.58-2.31)**	**1.24 (1.02-1.51)**
Blood pressure		
Normal	ref	ref
Hypertension	**2.46 (2.23-2.71)**	**1.36 (1.22-1.51)**

TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglycerides; 2h-FG: 2-hour plasma glucose; sdLDL-C: Small dense low-density lipoprotein cholesterol according to Sampson equation
The OR illustrated the weight analysis
The bold number was statistically significant; ref was the reference group.

Table 6 also showed the adjusted OR and 95% CI value, quintile 5 vs. quintile 1 of sdLDL-C and DM. The result shows that sdLDL-C and central obesity remained positively associated with DM status. The subject in the highest quintile had double the odds of DM (aOR; 1,98; 95% CI: 1.43-2.75) than the subject with the lowest quintile, while the subject with central obesity was observed at 1.34 times the odds of DM (95% CI: 1.17-1.53) than normal subjects. The highest quintile of sdLDL-C and central obesity was independently associated with DM.

DISCUSSION

The study showed a positive association between sdLDL-C and obesity and sdLDL-C and DM status. The result showed increasing mean plasma glucose across quintiles. It is similar to the previous study reported by Sriswasdi et al. [2] and Izumida et al. [3]. sdLDL-C was a subclass of type LDL-C. There are two types of LDL-C: pattern A [(large buoyant (lbLDL-C)] and pattern B [(small dense LDL-C (sdLDL-C)] [4]. sdLDL-C was considered an atherogenic subclass of LDL-C since its characteristic has a small size and more sustain in the artery wall [4] as the leading cause of vascular stiffening [5]. A crucial aspect led to cardiovascular diseases (CVD) is diabetic dyslipidemia or atherogenic dyslipidemia, which is signed by elevated sdLDL-C, elevated TG, and decreased HDL-C [6, 7]. Numerous conditions stimulated the raising of sdLDL-C, but the primary factor correlated with lipid profile abnormalities is obesity [8], especially central obesity [9].

A present study found that general obesity and central obesity were strongly correlated with sdLDL-C. The results showed that sdLDL-C level increased gradually with the value of BMI and waist circumference ($p < 0.001$). Furthermore, a smaller study in Thailand showed that 58% of the obese subject had LDL-C peak density (gr/ml) ≥1.033, which is considered sdDLDL-C [10], and the increment of sdLDL-C was also found in people with metabolic syndrome [9].

sdLDL-C is a lipoprotein fraction derived from very low-density lipoprotein (VLDL). Substrates for lipoprotein lipase-mediated triglyceride [11]. There are two subclasses of VLDL: VLDL 1 and VLDL 2. In generic conditions, VLDL 1 is lower than VLDL 2. VLDL 1 is TG-rich content as an essential substrate for hepatic lipase. Moreover, hydrolyzed TG becomes a small and high-density LDL-C [4, 11]. Commonly, people

with insulin resistance secreted VLDL 1 higher than usual [11]. The original mechanism is promoted by CETP (cholesteryl esters transfer protein), which transfers plasma TG from VLDL1 to LDL-C. At the same time, CETP transfers CE (cholesterol esters) from LDL to VLDL1 and develops TG-rich LDL-C. Then, sdLDL-C is formed from TG-rich LDL-C as a precursor [4, 6, 11].

This study analyzed the sociodemographic parameters associated with sdLDL-C and DM. The result showed that age, sex, place of living, occupation, education attainment, and economic status were strongly associated with sdLDL-C. Compared with the previous study that showed no association between sdLDL-C and age [12]. The variation in results is likely due to the respondent's varying age characteristics. sdLDL-C level in men tends to be higher than in women. It may be caused by the likelihood of smoking being higher among men than women. Current male smokers had higher sdLDL-C concentrations than women (34.6 vs. 25.0 mg/dl, respectively) [13]. The occupation except for farmer/fisher/laborer and the highest quintile of economic status tends to be higher in the sdLDL-C level, and obesity may be related to this issue. Individuals living in urban areas had a higher sdLDL-C level: urbanization may trigger lipid disorders [14]. It was proven by Mohan et al. that sdLDL-C was significantly higher in urban diabetic subjects [15]. This phenomenon indicated that the risk of DM is indistinguishable in urban and rural areas. Similarly, a study in Malaysia showed no significant association between place of living and DM [16]. We assumed dietary patterns in rural areas related to socioeconomic [17], high consumption of sugar [18], and access issues of public healthcare may play a role in this condition [19].

Behavior risk factors include smoking habits, physical activity, and dietary fruits and vegetables. All of them, however, were crucial factors in elevated sdLDL-C. Our study showed that a former smoker had a higher sdLDL-C. Nicotine may promote a rising VLDL via secreted hormones. cortisol and catecholamine. This condition, however, may trigger the increase of fatty acid and TG-rich lipoprotein, a precursor of sdLDL-C [13]. The study showed a positive association between former smokers and the risk of DM status, confirmed by the previous study in China [20, 21]. It may be associated with an overall cumulative exposure to smoking before quitting. Possibility judgment is the 'weight cycling' phenomenon that occurs in weight gain and the increase in waist circumference, influencing the development of insulin resistance [22]. The previous study showed that BMI was associated with insulin resistance [23]. On the contrary, there was a negative association between DM and current smokers: the more significant energy expenditure and suppressed appetite were possible mechanisms that directly impact nicotine on energy balance [22, 24].

Among subjects, a group meeting recommendation for physical activity was negatively associated with sdLDL-C and DM status. The experimental study showed that moderate physical activity changed the mean LDL-C particle. Consequently, lipid profile and oxidative stress status benefit from increasing the clearance of circulating sdLDL-C [25]. The present study showed no significant association between dietary fruits and vegetables and DM, in contrast to a large study showing that ≈5 servings of fruits and vegetables were associated with reduced mortality of chronic diseases [26]. Although there was no association between dietary fruits and vegetables in multivariate analysis, the negative association was demonstrated in correlational analysis.

In addition, the generic risk factors of DM are hypertension and increased creatinine level. Our finding of an association between hypertension and creatinine level showed consistency with the previous study [12, 27] a significant association between sdLDL-C, hypertension, and creatinine level. Table 3 shows mean systolic, diastolic, and creatinine levels across quintiles. It suggested that sdLDL-C has an intercorrelation role with other clinical parameters in developing DM.

This study determined sdLDL-C, central obesity, and DM. To the best of our knowledge, this is the first study to investigate the relationship between sdLDL-C, central obesity, and DM on a large, nationwide scale. Furthermore, the numerous limitations of our study must be noticed. First, our cross-sectional study cannot investigate the causality between sdLDL-C, central obesity, and DM. Second, we only used the formula to find sdLDL-C concentration, but it is more effective, cheaper, and less time-consuming than laboratory measurement.

Further studies in experimental laboratories may be needed. Furthermore, although the sample size adequately represents the Indonesian population, the formula may be efficiently used to estimate sdLDL-C at the population level. The result may need to be generalizable to other populations with an advanced study design that can answer the causality of sdLDL-C and DM.

CONCLUSION

In conclusion, our findings demonstrated an association between sdLDL-C, central obesity, and the development of DM. Comprehensive prevention in lifestyle modification, such as dietary patterns, and

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physical activity will be advantageous. The future multiethnic investigation of sdLDL-C, central obesity, and dietary pattern in Indonesia may be interesting.

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