

# Contribution and interaction of the low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and triglyceride to diabetes in hypertensive patients: A cross-sectional study

Mengyang Hong<sup>1,2</sup>, Yan Ling<sup>1</sup>, Zhiqiang Lu<sup>1</sup>, Ying Liu<sup>1</sup>, Ping Gu<sup>2</sup>, Jiaqing Shao<sup>2</sup>, Xin Gao<sup>1</sup>, Xiaomu Li<sup>1</sup>

<sup>1</sup>Department of Endocrinology & Metabolism, Zhongshan Hospital, Fudan University, Shanghai, and <sup>2</sup>Department of Endocrinology & Metabolism, Jingling Hospital, School of Medicine, Nanjing University, Nanjing, China

## Keywords

Diabetes, Hypertension, Lipid abnormality

## Correspondence

Xiaomu Li  
Tel/Fax: +86-21-6404-1990  
E-mail address:  
li.xiaomu@zs-hospital.sh.cn

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## ABSTRACT

**Aims/Introduction:** Hypertension is one of the most significant risk factors for diabetes. The present study aimed to investigate the associations of lipid profiles, including the ratio of low-density lipoprotein cholesterol (LDL-C)-to-high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels, as well as their interactions, with type 2 diabetes in hypertensive patients.

**Materials and Methods:** Hypertensive patients without a history of diabetes and hypolipidemic agents were enrolled continuously at the Hypertension Clinic, Zhongshan Hospital, Fudan University (Shanghai, China) from 2014 to 2016. General clinical data, including body mass index, blood pressure, fasting glucose and 2-h post-load glucose levels, and lipid profiles, were collected. The LDL-C/HDL-C ratio, TG/HDL-C ratio and TC/HDL-C ratio were separately calculated. Statistical analyses were carried out by using SPSS software (version 13.0).

**Results:** In total, 935 hypertensive patients were included, of which 114 patients (12.2%) were diagnosed with diabetes. After multivariate adjustments, the LDL-C/HDL-C ratio and TG levels had the most significant and independent associations with diabetes. In the multivariate logistic regression, the LDL-C/HDL-C ratio and TG were independently associated with diabetes. After the interaction variable was included, the LDL-C/HDL-C ratio remained independently associated with diabetes, but TG was replaced by TG\*LDL-C/HDL-C.

**Conclusions:** In conclusion, elevated LDL-C/HDL-C ratios and TG levels were associated with diabetes in patients with hypertension, with an interactive effect of the LDL-C/HDL-C ratio and TG on diabetes in the hypertensive population.

## INTRODUCTION

Hypertension and diabetes mellitus are independently associated with cardiovascular disease, and comorbidity of these two conditions might significantly increase this risk<sup>1</sup>. Blood pressure and glucose abnormalities have been previously identified as the two major independent factors related to the risk of all causes of mortality, especially cardiovascular-based mortality<sup>2</sup>.

Hypertension is also among the most important risk factors for diabetes<sup>3</sup>, with hypertensive individuals having an increased risk of developing incident diabetes<sup>4</sup>. The concurrence of hypertension and diabetes might be an important public health concern in the prevention of cardiovascular disease. Type 2 diabetes might be prevented and delayed by identifying and intervening in common risk factors at early stages of this condition. Although diabetes is a typical multifactorial disease, studies analyzing other risk factors (in addition to blood pressure) for the

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development of diabetes in hypertensive patients are limited. Antihypertension medications, including beta-blockers and diuretics, have been reported to be associated with the risk of incident diabetes<sup>5,6</sup>. Carotid atherosclerosis and left ventricular hypertrophy have been recently reported to be significant independent predictors of diabetes in a population of hypertensive patients<sup>7</sup>. Identifying additional common risk factors for diabetes remains important for preventing diabetes and cardiovascular disease in the hypertensive population.

Dyslipidemia is known as a risk factor for type 2 diabetes in the general population. Disturbances in lipid metabolism might be an early incident in the development of diabetes; triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) levels were previously identified to be associated with the incidence of diabetes<sup>8</sup>. Blood pressure and TG levels have also been reported to be independently associated with the development of incident diabetes in a middle-aged Norwegian cohort<sup>9</sup>. These studies from a general population suggested that TG might increase the risk of diabetes independent of other factors, including blood pressure; this possibility should be further investigated in the hypertensive population. Furthermore, recent evidence has shown that the ratio of low-density lipoprotein cholesterol (LDL-C)/HDL-C, which can be directly calculated from lipid profiles, is a prior marker of insulin resistance compared with the conventional lipid measurements<sup>10</sup>. Although traditional lipid measurements have been well established to be associated with type 2 diabetes, studies on the association of the LDL-C/HDL-C ratio with diabetes are still limited. It would be of interest to investigate the utility of lipid profiles (including traditional measurements and calculated ratios) in assessing the risk of type 2 diabetes in hypertensive patients. In the present study, we explored the association and interaction of these lipid profiles, especially on the LDL-C/HDL-C ratio and TG, with type 2 diabetes in 935 hypertensive patients.

## METHODS

### Ethics, consent and permission

All procedures were carried out in compliance with the Helsinki Declaration. The present study was approved by Zhongshan Hospital ethics committee, Fudan University, China. All the participants signed the informed consent.

### Study population

Patients with essential hypertension were continuously enrolled from the Zhongshan Hospital Hypertension Clinic, Fudan University, Shanghai, China, from 2013 to 2014. All the patients were previously diagnosed hypertensive patients, have received antihypertension medications and met the 1999 World Health Organization/International Society of Hypertension criteria<sup>11</sup>. Secondary forms of hypertension were ruled out by routine examinations. Patients who had a history of diabetes or who were taking hypoglycemic medications, as well as patients who were using lipemic-modulating agents were also excluded. The total number of enrolled participants included in the

present study was 935 essential hypertension patients. We used the 1999 World Health Organization criteria for diabetes<sup>12</sup> to diagnose diabetes patients. Either a fasting plasma glucose  $\geq 7.0$  mmol/L or a 2-h post-load glucose  $\geq 11.1$  mmol/L was defined as diabetes. The homeostatic model assessment of pancreatic  $\beta$ -cell function (HOMA- $\beta$ ) and the homeostatic model assessment of insulin sensitivity (HOMA-IR) were estimated using Levy's computer model<sup>13</sup>. Glutamic acid decarboxylase antibody was tested in all diabetes patients to screen for type 1 diabetes.

### General clinical data collection

The patients' demographic data, including age, sex, family history of diabetes, duration of hypertension and medication history, were obtained from the clinical documents at the hypertension clinic. According to the routine protocol, a complete physical examination, including measurement of the patients' height, weight, waist circumference and blood pressure, was carried out. Anthropometric measures were collected by trained nurses. Weight (kg) and height (m) were measured with patients wearing only underwear. The body mass index (BMI;  $\text{weight}/\text{height}^2$ ) was calculated. Waist circumferences was measured using a tape at the smallest horizontal circumference between the costal margin and iliac crests. Systolic blood pressure (SBP) and diastolic blood pressure were measured by a nurse with a mercury sphygmomanometer adapted for arm size after 5 min of rest with the participants in the sitting position. Two blood pressure measurements were recorded at 5-min intervals, the means were used for the data analysis.

After overnight fasting for 10 h, a 75-g glucose tolerance test was carried out, and blood samples were collected both during fasting and 120 min after administration of the glucose load. The glucose oxidase method was used to measure the plasma glucose levels; a radioimmunoassay method, for serum insulin levels. Standard enzymatic tests were used for fasting lipid profiles (total cholesterol [TC], TG and HDL-C). LDL-C concentration was calculated as TC minus the cholesterol in the supernatant by the precipitation method using the Friedewald equation, non-HDL-C was calculated by subtracting HDL-C from TC, and the TC/HDL-C ratio, TG/HDL-C ratio and LDL-C/HDL-C ratio were separately calculated.

### Statistical analysis

Normally distributed continuous variables are expressed as the mean  $\pm$  standard deviation; the non-normal variables are expressed as the median with the interquartile range. Non-normal values were log-transformed before analysis, and were carried out with Student's *t*-test or the  $\chi^2$ -test for normally distributed continuous and categorical variables, respectively. Partial Spearman's correlation analysis was used to determine the correlation among the lipid profiles. We analyzed the association of the lipid profiles with diabetes by multivariate logistic regression in different models. The associations of the lipid profiles with blood glucose levels were analyzed by using

**Table 1** | General characteristic of hypertensive patients with or without diabetes

Variables	All (n = 935)	Non-diabetes (n = 821)	Diabetes (n = 114)	P-value
Age (years)	59.5 ± 9.9	59.4 ± 10	60.4 ± 9.4	>0.05
Sex (M/F)	414/521	357/464	57/57	>0.05
BMI	25.27 ± 3.28	25.11 ± 3.21	26.43 ± 3.5	<0.05
WC (cm)	86 ± 10	85 ± 10	89 ± 10	<0.05
SBP (mmHg)	140.42 ± 18.01	139.82 ± 17.69	144.65 ± 19.68	<0.05
DBP (mmHg)	84.01 ± 10.31	83.72 ± 10.21	86.04 ± 10.81	<0.05
TC (mmol/L) Male	4.7 ± 0.2	4.7 ± 0.1	4.9 ± 0.1	>0.05
Female	5.2 ± 0.1	5.2 ± 0.2	5.4 ± 0.2	>0.05
TG (mmol/L)	1.8 ± 1.4	1.7 ± 1	2.4 ± 2.8	<0.05
LDL-C (mmol/L)	2.9 ± 0.8	2.9 ± 0.8	2.9 ± 0.9	>0.05
HDL-C (mmol/L)	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	<0.05
Non-HDL-C (mmol/L)	3.62 ± 0.92	3.58 ± 0.89	3.89 ± 1.07	<0.05
TC/HDL-C	3.84 ± 0.97	3.78 ± 0.94	4.25 ± 1.1	<0.05
TG/HDL-C	1.47 ± 1.27	1.39 ± 1.10	2.08 ± 1.94	<0.05
LDL-C/HDL-C	2.2 ± 0.71	2.17 ± 0.7	2.39 ± 0.77	<0.05
FBG (mmol/L)	5.3 ± 0.9	5.1 ± 0.6	6.7 ± 1.4	<0.05
2hPG (mmol/L)	7.8 ± 2.9	7 ± 1.8	13.5 ± 3.3	<0.05
Fins+ (mU/L)	18.1 (13.2–24.9)	17.7 (12.9–24.6)	21.8 (15.3–29.3)	<0.05
Pins+ (mU/L)	92.1 (61.2–133.9)	87.1 (59.2–128.3)	131.3 (82.8–184.6)	<0.05
HOMA-IR+	4.2 (3.0–6.2)	3.9 (2.9–5.7)	6.2 (4.3–8.1)	<0.05
HOMA-β+	228.7 (160.2–329)	232.8 (165.2–341.2)	175.6 (98.8–287.4)	<0.05

Continuous data are expressed as mean ± standard deviation. +, Variables were log-transformed before statistical analysis; numbers in the table were back-transformed as median (inter quartile range). P-value for comparison between diabetes and non-diabetes groups, adjusted for age except age and percentage of men. 2hPG, 2-h plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; F, female; FBG, fasting blood glucose; Fins, fasting insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-β, homeostatic model assessment for β-cell function; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; M, male; Pins, 2-h insulin; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

multivariate linear regression. To further evaluate the interactive effect of TG and the LDL-C/HDL-C ratio, a new term (TG × LDL-C/HDL-C ratio) was calculated and included in the relevant regression models as an additional variable. We further evaluated the joint effect of TG and the LDL-C/HDL-C ratio on diabetes by dividing the study population into nine groups, which were defined by the combinations of the TG and LDL-C/HDL-C ratio tertiles. The adjusted odd ratios for diabetes were obtained using a multiple logistic regression model, with patients with TG <2.5 mmol/L and an LDL-C/HDL-C ratio <1.9 defined as the reference group. All statistical tests were two-tailed, and  $P < 0.05$  was considered as statistically significant. The analyses were carried out by SPSS software (version 13.0; SPSS, Chicago, IL, USA).

## RESULTS

The characteristics of the participants are presented in Table 1. Among the 935 hypertensive patients, 114 patients (12.2%) were diagnosed with diabetes in the present study (all the patients were glutamic acid decarboxylase antibody-negative, data not shown). The diabetes patients had a higher BMI, larger waist circumferences and increased levels of SBP, diastolic blood pressure, TG, non-HDL-C, TC/HDL-C, TG/HDL-C and LDL-C/HDL-C, as well as lower HDL-C levels ( $P < 0.05$ )

compared with the non-diabetes patients. The TC, LDL, age levels and sex distribution were similar between these groups (Table 1).

Strong correlations were found among the TC, LDL-C and non-HDL-C levels, ranging from 0.81 to 0.94. The TC/LDL-C and LDL-C/HDL-C ratios were also strongly correlated ( $r = 0.86$ ). The correlations of TG to other lipid profiles were moderate, ranging from 0.10–0.53 (data not shown).

The odds ratios (ORs) for diabetes in hypertensive patients according to the increasing tertiles of each lipid variable are shown in Table 2. After multivariate adjustments for age, sex, BMI, BP levels, antihypertensive medications, smoking status and family history of diabetes, the two lipid ratios (including TC/LDL-C and LDL-C/HDL-C) had significant associations with diabetes in hypertensive patients (OR in the highest tertile 2.19 or 1.95, respectively;  $P < 0.01$  for the trend across all tertiles). Among the single lipid markers, the TG and HDL-C levels also showed strong associations with diabetes in hypertensive patients (OR in the highest tertile 2.18 or 0.5, respectively;  $P < 0.05$  for the trend across all tertiles).

To investigate the potential independent risk factors for diabetes among the lipid profiles in hypertensive patients, a multivariate stepwise logistic regression was carried out (Table 3). After multivariate adjustments for age, sex, BMI, BP levels,

**Table 2** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles

	Tertile 1	Tertile 2	Tertile 3	<i>P</i> for trend
TC, mmol/L (range)	<4.6	4.6–5.3	>5.3	
Male				
No. DM	22 (11.9%)	16 (12.8%)	19 (20.4%)	
Model 1	1.00	1.03 (0.72–1.91)	1.55 (1.01–2.59)	0.098
Model 2	1.00	1.00 (0.43–2.12)	2.03 (1.02–3.96)	0.082
Female				
TC, mmol/L (range)				
No. DM	13 (10.7%)	17 (9.7%)	27 (12.3%)	
Model 1	1.00	0.90 (0.49–2.23)	1.32 (0.59–2.99)	0.454
Model 2	1.00	0.96 (0.40–2.36)	1.19 (0.78–2.87)	0.717
TG, mmol/L (range)	<1.2	1.2–1.8	>1.8	
No. DM	24 (7.6%)	35 (11.3%)	55 (17.7%)	
Model 1	1.00	1.50 (0.87–2.59)	2.62 (1.57–4.36)	<0.001
Model 2	1.00	1.28 (0.73–2.24)	2.18 (1.30–3.67)	0.002
LDL-C, mmol/L (range)	<2.5	2.5–3.2	>3.2	
No. DM	34 (10.9%)	36 (11.5%)	44 (14.2%)	0.143
Model 1	1.00	1.13 (0.68–1.86)	1.43 (0.88–2.33)	0.170
Model 2	1.00	1.13 (0.68–1.87)	1.41 (0.86–2.31)	
HDL-C, mmol/L (range)	<1.2	1.2–1.5	>1.5	
No. DM	58 (16.0%)	33 (12.6%)	23 (7.4%)	
Model 1	1.00	0.75 (0.47–1.21)	0.42 (0.25–0.72)	0.002
Model 2	1.00	0.81 (0.50–1.31)	0.50 (0.29–0.88)	0.017
Non-HDL-C, mmol/L (range)	<3.3	3.3–4.0	>4.0	
No. DM	32 (10.2%)	33 (10.6%)	49 (15.8%)	
Model 1	1.00	1.08 (0.65–1.82)	1.71 (1.06–2.76)	0.025
Model 2	1.00	1.02 (0.60–1.72)	1.58 (0.97–2.57)	0.056
TC/HDL-C ratio (range)	<3.4	3.4–4.2	>4.2	
No. DM	21 (6.8%)	42 (13.5%)	51 (16.3%)	
Model 1	1.00	2.13 (1.23–3.70)	2.64 (1.53–4.53)	0.001
Model 2	1.00	1.84 (1.05–3.23)	2.19 (1.26–3.81)	0.007
LDL-C/HDL-C ratio (range)	<1.9	1.9–2.5	>2.5	
No. DM	27 (8.7%)	31 (10.0%)	56 (17.9%)	
Model 1	1.00	1.17 (0.68–2.01)	2.24 (1.37–3.68)	0.001
Model 2	1.00	1.03 (0.60–1.80)	1.95 (1.18–3.22)	0.006

Model 1: adjusted for age and sex. Model 2: as for model 1 plus body mass index, blood pressure levels, antihypertensive medications, smoking status and family history of diabetes. CI, confidence interval; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TC, total cholesterol; TG, triglyceride.

antihypertensive medications, smoking status and family history of diabetes, TG levels and LDL-C/HDL-C ratio were the only two variables independently associated with diabetes in hypertensive patients (OR in the highest tertile 2.22 or 1.82, respectively; *P* for trend < 0.05). After the interaction variable TG × LDL-C/HDL-C was included, TG was excluded from the final model in favor of the TG × LDL-C/HDL-C ratio (OR in the highest tertile 1.60, *P* for trend = 0.033), but the LDL-C/HDL-C ratio (OR 1.09, *P* for trend = 0.001) remained associated with diabetes. As shown in Figure 1, the TG levels were significantly associated with HOMA-IR (*P* < 0.001), and the association of the LDL-C/HDL-C ratio with HOMA-β was borderline significant (*P* = 0.05).

A stepwise linear regression analysis was carried out considering fasting blood glucose and 2-h plasma glucose as the

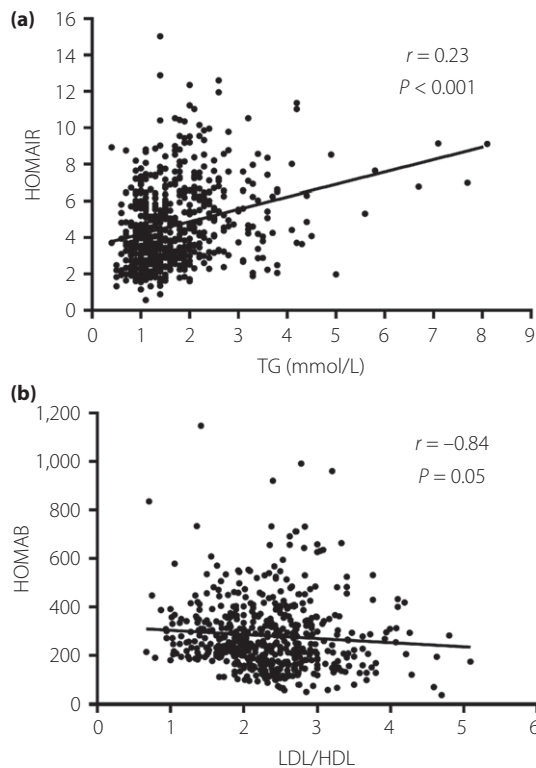
dependent variables, and the lipid profiles and other metabolic profiles as the independent variables, adjusting for age, sex, antihypertensive medication status, smoking status and family history of diabetes. The results showed that the TG, BMI and SBP were significantly correlated with fasting blood glucose levels, whereas the TG, LDL-C/HDL-C ratio, BMI and SBP were independently associated with 2-h plasma glucose. After the interaction variable was included in the full model, the TG levels and LDL-C/HDL-C ratio were both replaced by TG × LDL-C/HDL-C, which was independently associated with 2-h plasma glucose levels (Table 4).

In the joint analyses, we computed the ORs for diabetes in a multiple logistic regression model in which combinations of TG and LDL-C/HDL-C ratio tertiles were used to reclassify the participants into nine subgroups. Individuals in the highest

**Table 3** | Logistic regression analysis of the associations of lipid profiles with diabetes mellitus in essential hypertension

	Model 1 OR (95%CI)	P for trend	Model 2 OR (95%CI)	P for trend	Model 3 OR (95%CI)	P for trend
TG tertile 1	1.00		1.00			
TG tertile 2	1.16 (0.65–2.06)		1.32 (0.75–2.32)			
TG tertile 3	1.89 (1.10–3.24)	0.002	2.22 (1.30–3.77)	0.01	–	
LDL-C/HDL-C tertile 1	1.00		1.00			
LDL-C/HDL-C tertile 2	0.97 (0.55–1.70)		1.04 (0.59–1.80)		0.99 (0.57–1.72)	
LDL-C/HDL-C tertile 3	1.70 (1.01–2.88)	0.010	1.82 (1.09–3.06)	0.03	1.60 (0.93–2.74)	0.033
TG × (LDL-C/HDL-C)	–		–		1.09 (1.04–1.16)	0.001

Odds ratio (OR) and 95% confidence interval (CI) are compared with the first tertile of each lipid profile. Model 1: total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL, TC/HDL-C ratio and LDL-C/HDL-C ratio were included, adjusted for age and sex. Model 2: TC, TG, LDL-C, HDL-C, non-HDL-C, TC/HDL-C ratio and LDL-C/HDL-C ratio were included, adjusted for age, sex, body mass index, blood pressure levels, antihypertensive medications, smoking status and family history of diabetes. Model 3: TC, TG, LDL-C, HDL-C, non-HDL, TC/HDL-C ratio, LDL-C/HDL-C ratio and TG × LDL-C/HDL-C ratio was included, adjusted for age, sex, body mass index, blood pressure levels, antihypertensive medications, smoking status and family history of diabetes.



**Figure 1** | Correlation of triglyceride (TG) levels with homeostatic model assessment of insulin resistance (HOMA-IR) and of the low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio with homeostatic model assessment of  $\beta$ -cell function (HOMA- $\beta$ ). (a) TG levels were significantly correlated with HOMA-IR, and (b) the LDL-C/HDL-C ratio was borderline correlated with HOMA- $\beta$ . HOMA-IR and HOMA- $\beta$  were log-transformed before statistical analysis; the values in the figure were back-transformed.

tertile of both the TG levels and LDL-C/HDL-C ratio had more than sixfold odds of diabetes compared with those in the lowest tertiles of both variables (OR 6.12, 95% confidence interval

1.98–9.30). Hypertensive patients with elevated TG levels and LDL-C/HDL-C ratio tended to have a higher odds of diabetes ( $P < 0.01$  for the trend across all tertiles; Figure 2).

In addition, further analysis was carried out in three pairs of subgroups, including in patients with or without the use of beta-blockers or diuretics, male or female and with or without the history of smoking (Tables S1 and S2). The differences of age, sex, blood pressure control, lipid profiles and glucose levels were not significant between these subgroups ( $P > 0.05$ ). The results also showed that several lipid profile parameters, including TG, HDL-C, non-HDL-C, TC/HDL-C and LDL-C/HDL-C, were significantly associated with diabetes in subgroups without the use of beta-blockers or diuretics, and in subgroups without a history of smoking ( $P < 0.05$ ). In patients taking beta-blockers or diuretics, and in patients with a history of smoking, these associations did not reach a significant difference. Non-HDL and LDL-C/HDL-C were significantly associated with diabetes in men. TG, HDL-C and LDL-C/HDL-C were significantly associated with diabetes in women ( $P < 0.05$ ).

## DISCUSSION

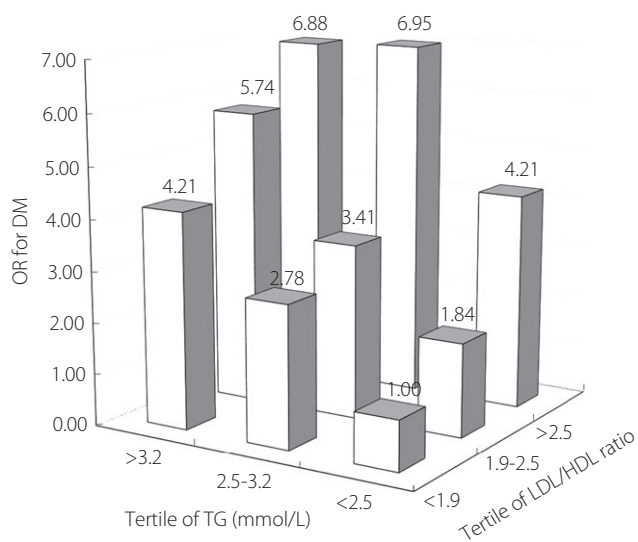
The present cross-sectional study of a hypertensive population showed that both TG and the LDL-C/HDL-C ratio were independently correlated with diabetes. The unreported interactive effects of TG and the LDL-C/HDL-C ratio with diabetes were also shown in these hypertensive patients. Participants with increased TG and an elevated LDL-C/HDL-C ratio had significantly higher odds of diabetes than other individuals. The interaction between increased TG levels and an elevated LDL-C/HDL-C ratio suggests that the accumulation of abnormal lipid profiles might interact with and exaggerate the risk of diabetes in hypertensive patients.

In the multiple regression model, we found a total of four lipid profiles with strong associations with diabetes in hypertensive patients, including two lipid ratios (TC/LDL-C and LDL-C/HDL-C) and two single lipid markers (HDL-C and TG). Considering the strong correlations of these lipid profiles (data

**Table 4** | Multivariate linear regression for glucose homeostasis in hypertension patients

	FBG						2hPG					
	Model 1			Model 2			Model 1			Model 2		
	$\beta$ adj	SEM	P-value	$\beta$ adj	SEM	P-value	$\beta$ adj	SEM	P-value	$\beta$ adj	SEM	P-value
TG	0.141	0.02	<0.001	0.141	0.02	<0.001	0.295	0.066	<0.001	–	–	–
LDL-C/HDL-C	–	–	–	–	–	–	0.442	0.132	0.001	–	–	–
BMI	0.043	0.009	<0.001	0.043	0.009	<0.001	0.129	0.029	<0.001	0.138	0.029	<0.001
SBP	0.005	0.002	0.004	0.005	0.002	0.004	0.024	0.005	<0.001	0.024	0.005	<0.001
TG $\times$ LDL-C/HDL-C	–	–	–	–	–	–	–	–	–	0.159	0.033	<0.001

Model 1: total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, TC to HDL-C ratio, LDL-C/HDL-C ratio were included, adjusted for age, sex, body mass index, blood pressure levels, antihypertensive medications, smoking status and family history of diabetes. Model 2: TG  $\times$  LDL-C/HDL-C ratio was included plus model 1.  $\beta$ adj, Adjusted regression coefficient; SEM, standard error.



**Figure 2** | Combination effect of triglyceride (TG) levels and the low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio on diabetes. Combinations of TG levels and the LDL-C/HDL-C ratio tertiles were used to reclassify the participants into nine subgroups. The odds ratios for diabetes were obtained with participants with TG <2.5 mmol/L and LDL-C/HDL-C <1.9 defined as the reference group.

not shown), further multivariable stepwise logistic analysis showed that only TG and the LDL-C/HDL-C ratio were independently associated with diabetes in hypertensive populations, and other profiles were eventually excluded from this model.

As a well-established cardiovascular risk factor and a traditional component in metabolic syndrome, TG levels are closely related to diabetes. It has been reported that the reduction in TG levels was associated with decreased diabetes risk in a cohort from Norway<sup>14</sup>. Elevated fasting triglycerides also predict impaired glucose tolerance in adolescents at risk for type 2 diabetes in America<sup>15</sup>. However, this association has not been

clearly shown in hypertensive patients with a high risk of developing diabetes. Furthermore, TG levels, which were calculated by the HOMA-IR index, were reported to be significantly associated with insulin resistance in a Chinese general population<sup>16</sup>. Acute lipid overload, which leads to hypertriglyceridemia, might cause skeletal muscle insulin resistance through mitochondrial dysfunction<sup>16</sup>. In the present study, we reported a correlation of TG levels with HOMA-IR, which suggested that the higher TG in hypertensive patients might be related to decreased insulin sensitivity and hyperglycemia. However, the TG/HDL-C ratio, which has been well established as a marker for insulin resistance<sup>17</sup>, was not included in the multivariable analysis models.

The LDL-C/HDL-C ratio was recently identified as a useful marker for predicting cardiovascular events and the progression of coronary artery disease<sup>18–20</sup>. However, the relationship of the LDL-C/HDL-C ratio to diabetes was still unclear. *In vitro* studies have suggested that LDL-C and HDL-C both affect  $\beta$ -cell function; HDL-C might increase acute insulin secretion, whereas LDL-C might inhibit insulin secretion in isolated islets or cultured beta cells<sup>21,22</sup>. Furthermore, HDL-C can also protect against the decreased insulin secretion caused by ox-LDL in cultured  $\beta$ -cells<sup>23</sup>. In addition, HDL-C and LDL-C also had adverse effects on  $\beta$ -cell survival, as HDL-C might decrease the number of cultured  $\beta$ -cells through LDL-induced apoptosis<sup>21,24</sup>. The present results suggested a borderline association of the LDL-C/HDL-C ratio with HOMA- $\beta$ , which indicates that the patients with a higher LDL-C/HDL-C ratio might have  $\beta$ -cell dysfunction related to diabetes within the hypertensive population.

From the joint analyses, the present results suggested that accumulated abnormal lipid profiles and their interactive effects might exaggerate the presence of glucose metabolic disorder and be related to diabetes in hypertensive patients. A combined assessment of TG levels and the LDL-C/HDL-C ratio might be associated with hypertensive patients with diabetes. Uppsala Longitudinal Study of Adult Men showed that low HDL-C is a

long-term predictor of insulin sensitivity<sup>25</sup>. Bezafibrate, which might reduce serum triglyceride and raise HDL-C, was found to be beneficial for delaying the development of pre-diabetes into diabetes<sup>26</sup>, and reduce HOMA-IR values and delay onset of insulin resistance<sup>27</sup>. In addition, accumulation of cholesterol content markedly influenced  $\beta$ -cell function, and an increased proportion of small dense LDL-C is associated with the accumulation of cholesterol in  $\beta$ -cells and decreased insulin secretion<sup>28–31</sup>. Taken together, the present results about the interactive effects of lipid profiles also showed that multidyslipidemia was significantly associated with diabetes, which might be mediated by both insulin resistance and  $\beta$ -cell dysfunction.

In addition, considering the significant effects of antihypertensive medication, sex and smoking<sup>32,33</sup> on the incidence of diabetes, analysis on the relative subgroups was carried out. The results from the subgroups not taking beta-blockers or diuretics and subgroups without a history of smoking were similar to the whole population. Because of the limited sample size and more confounding factors, no lipid profiles were significantly associated with diabetes in patients taking beta-blockers/diuretics or with a history of smoking.

A major limitation of the present study was the cross-sectional study design. Therefore, a causal relationship of TG levels and the LDL-C/HDL-C ratio to diabetes cannot be established in this Chinese hypertensive population. In addition, the present findings were based on a hospital-based study, whereas a further prospective cohort study in a population-based sample is necessary to clarify this relationship.

In conclusion, the present study showed that lipid profiles, including increased TG levels and LDL-C/HDL-C ratios, were independently correlated with diabetes in a Chinese hypertensive population. Furthermore, TG and the LDL-C/HDL-C ratio had an interactive effect on diabetes in hypertensive individuals. The present findings might provide a new insight on controlling multiple lipid profiles in patients with hypertension and diabetes.

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## DISCLOSURE

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1-1** | Clinical characteristics in patients with or without using beta-blockers or diuretics.

**Table S1-2** | Clinical characteristics in patients with or without a history of smoking.

**Table S1-3** | Clinical characteristics in male or female participants.

**Table S2-1** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles in patients not using beta-blockers or diuretics.

**Table S2-2** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles in patients using beta-blockers or diuretics.

**Table S2-3** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles in patients without a history of smoking.

**Table S2-4** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles in patients with a history of smoking.

**Table S2-5** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles in male participants.

**Table S2-6** | Odds ratio (95% confidence interval) for diabetes in essential hypertension according to lipid profiles tertiles in female participants.