Elevated remnant cholesterol is closely associated with incident hypertension: a cohort-based study from China

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Abstract

Background

Remnant cholesterol (RC) has been confirmed to be associated with cardiovascular events. However, the association between RC and hypertension (HTN) has not been illustrated. Thus, this study aimed to investigate the association of RC with HTN and to compare the predictive values of RC, lipid parameters for the risk of incident HTN in a Chinese population.

Methods

This cohort study included 18483 participants, who are followed for the incidence of HTN. RC were divided into five groups: the < 20% group, the 20–39% group, the 40–59% group, the 60–79% group and the ≥ 80% group, according to quintile division of the participants. Cox proportional hazards models were used to evaluate the association between RC vs other lipid parameters and HTN.

Results

During a mean follow-up of 1.1 years, 525 (17.55%) HTN occurred. Multivariate Cox regression analysis shows that compared with conventional lipid parameters, RC remains significantly associated with HTN (hazard ratio (HR) 1.68, 95% confidence interval (CI) 1.40-2.01, p<0.0001). In a stratified analysis, RC is still significant predictive of developing HTN in the subgroups of young age (<55 years) (HR 1.74, 95% CI 1.40-2.16, p<0.0001), as well as with body mass index (BMI) <18.5 kg/m^2 (HR 2.87, 95%CI 1.30-6.37, p=0.0464) or BMI ≥ 28 kg/m^2 (HR 1.81, 95%CI 1.11-2.96, p=0.0179), and with fatty liver diseases (HR 1.66, 95% CI 1.17-2.36, p=0.0047).

Conclusions

Elevated RC is significantly associated with HTN and is a superior predictor for developing HTN independent of other risk factors, suggesting RC may be a new target of managing HTN.

Background

Hypertension (HTN) is the most prevalent risk factor for cardiovascular diseases (CVDs) internationally and evidence from published studies shows that over 33% of the world’s population has been affected by HTN\(^1,2\). In China, the prevalence of HTN is rising in recent decades, which has been a national public health burden and priority\(^3\). About 50% of the Chinese adults aged over 35 years have HTN, leading to an increasing mortality related with high blood pressure and CVDs\(^4,5\).

Lipid abnormalities has been widely confirmed associated with HTN, and both of them are important risk factors for CVDs. It is reported that coexistence of dyslipidemia and HTN is often observed and over 50% hypertensive patients has been diagnosed with dyslipidemia in clinical practice\(^6,7\). Dyslipidemia is defined as elevated triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C), independently associated with HTN and CVDs\(^8,9\).
Evidence from epidemiological and genetic research has engendered new interests that are demonstrating abnormal TG, LDL-C, lipoprotein(a) (Lp(a)), or TG-rich lipoproteins (TGRLs) are additional risk factors for atherosclerosis cardiovascular diseases (ASCVD)-related death\textsuperscript{10-13}. It is reported that LDL-C is associated with CVDs risk, and lowering LDL-C in desired range could reduce the risk of CVDs due to the achieved reduction in LDL-C\textsuperscript{14}. Similarly, lowering TG reduces the risk of CVDs, equal to LDL-C-lowering therapies\textsuperscript{15}. Furthermore, a follow-up study of 5971 women found a significant association between lipid parameters and HTN, and researches based on adolescents reached similar results\textsuperscript{16,17}. However, recurrent CVDs is still a major cause of mortality worldwide though achieving optimal LDL-C level in clinical practice\textsuperscript{18,19}. TGRLs and their cholesterol content, known as remnant cholesterol (RC), has been revealed contributing to the residual risk of CVDs\textsuperscript{20,21}.

RC is the cholesterol content of TGRLs, comprising of chylomicron remnants (CR), very low-density lipoprotein (VLDL), and intermediate density lipoprotein (IDL)\textsuperscript{22}. Emerging data has reported a genetic association between increased RC and CVDs \textsuperscript{23,24}. Although previous clinical studies have observed a significant association between RC and cardiovascular events, studies about the predictive implications of RC and HTN in the Chinese population is still lacking\textsuperscript{25}. Moreover, studies are limited that involve the comparison of predictive abilities of RC and other individual lipid parameters for the risk of HTN. Thus, the aim of our study is to explore the association between RC and HTN and compare the predictive power of RC and lipid parameters for HTN in the Chinese population.

**Methods**

**Study population**

The present study included 42,994 individuals who participated in physical examination from April 2016 to August 2020 and follow-up during April 2017 to August 2021 in Dalian of China. The exclusion criteria as follows: previous history of HTN, current diagnosed with HTN, other previous history of related chronic diseases, using related drugs, missing detailed data and/or included outliers. Finally, 18,483 individuals were recruited (Fig. 1).

**Baseline data collection**

All participants who were recruited underwent detailed clinical examination by experienced physicians as well as anthropometric measurements. The medication history was defined based on the self-reported history of diabetes, HTN, dyslipidemia, kidney diseases, hepatic diseases, the current use of drugs, drinking and smoking habits. Blood pressure were recorded twice at 1-minute intervals by the same staff when participants were in a seated position for a five-minutes rest.

Blood samples were obtained from the antecubital vein after \(\geq 8\) hours of overnight fasting and stored at \(-80\) °C until analysis. Fasting plasma glucose (FPG), TG, TC, HDL-C, LDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine (Cr) were measured. The estimated glomerular
filtration rate (eGFR) was expressed in mL/min per 1.73 m² using the formula, eGFR = 175 × (serum Cr in mg/dL)⁻¹.154 × age⁻⁰.₂⁰₃ × (0.742 for women) × (1.212 if African American)²⁶. RC was evaluated using the formula: RC = TC - HDL-C - LDL-C²⁷.

Follow-up examination

The endpoint outcome of this current study was the incidence of HTN during the follow-up period. Participants were followed up for a median of 1.1 years using annual medical checkup data that is collected between April 2017 and August 2021.

Definition of variables

RC was divided into five groups: the < 20% group, the 20–39% group, the 40–59% group, the 60–79% group and the ≥ 80% group, based on quintile division of the participants. According to the Chinese guideline for the management of dyslipidemia in adults (revised in 2016), lipid parameters were categorized into several groups as follows: TG: normal: < 1.7 mmol/L, borderline: 1.7–2.3 mmol/L, high: ≥ 2.3 mmol/L; TC: normal: < 5.2 mmol/L, borderline: 5.2–6.2 mmol/L, high: ≥ 6.2 mmol/L; HDL-C: desired: ≥ 1.0 mmol/L, high: < 1.0 mmol/L; 4. LDL-C: ideal < 2.6 mmol/L, borderline: 3.4–4.1 mmol/L, high: ≥ 4.1 mmol/L²⁸. HTN was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or diagnosed history of HTN by clinicians and meanwhile taking antihypertensive medication. Fatty liver disease was defined as hepatic steatosis was confirmed by hepatic ultrasonography. Body mass index (BMI) was calculated using the following formula: BMI = body weight/ height² (kg/m²). Drinkers were defined as participants who regularly consumed alcohol in the past years. Smokers were defined as participants who regularly smoked at least one cigarette in the past years.

Statistical analysis

Empower(R) (www.empowerstats.com, X&Y Solutions Inc., Boston, MA) and R (http://www.Rproject.org) were used to perform the statistical analyses. The hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were calculated. All statistical tests were two-sided, and P values < 0.05 were considered statistically significant.

Continuous variables with a non-normal distribution were shown as median (Q1-Q3), and those with a normal distribution were shown as means ± the standard deviations (SD). Categorical variables were presented as n%. Kruskal–Wallis test was used to assess the differences in continuous variables, and the χ² test was used in categorical variables were. Cox proportional hazards analysis was performed to evaluate the associations of RC, individual lipid parameters with HTN in multivariate settings with adjustments for potential confounding factors. Five models were built to investigate the associations between RC, lipid parameters and HTN. Model 0 was unadjusted. Model 1 was adjusted for age and sex. Model 2 was adjusted for baseline BMI, ALT, AST, eGFR based on Model1. Model 3 was additionally adjusted for FBG
based on Model 2. Model 4 was further adjusted for smoking habits and drinking habits based on Model 3. Stratified analyses were performed by age (G1: < 55, G2: 55–65, G3: ≥ 65), BMI (underweight: < 18.5 kg/m\(^2\); normal weight: 18.5–24 kg/m\(^2\); overweight: 24–28 kg/m\(^2\), obesity: BMI of ≥ 28 kg/m\(^2\), based on Cooperative Meta-analysis Group of China Obesity Task Force report\(^{26}\)) and fatty liver diseases (Yes and No).

**Results**

**Baseline characteristics of the study population**

The baseline characteristics of 18,483 participants (10,446 men and 9219 women) with a mean age (Q1-Q3) of 37.00 (31.00-48.00) years was shown in Table 1. With the increase in RC levels, BMI, SBP, DBP, FBG, TC, TG, LDL-C, ALT, AST significantly increased, and HDL-C, eGFR significantly decreased. The percentiles of smoking and drinking habits were highest in the highest quintile of RC (Q5). Also, the incidence of HTN 525 (17.55%) during follow-up period was highest in participants with increased RC levels (Q5).

**Factors associated with the incidence of HTN**

Univariate analysis revealed that age, BMI, RC, TC, TG, LDL-C and FBG were positively correlated with the incidence of HTN, while HDL-C were negatively correlated with the incidence of HTN. In univariate analysis, RC presented the closest association with the incidence of HTN, as shown in Table 2.

**Associations of RC, lipid parameters with HTN**

Multivariate Cox regression models was constructed to investigate the predictive ability of RC and individual lipid profiles with the incidence of HTN. Table 3 shows the HR and 95% CI of the incidence of HTN with the groups of RC quintiles, TG, TC, HDL-C, and LDL-C in the total population within five models. As shown in Table 3, RC and other lipid parameters all presented a significant association with HTN in non-adjusted model and Model 1 adjusting for age and BMI. Further adjustments for ALT, AST, eGFR, FBG and smoking, drinking habits in Model 4, only RC quintiles, TG groups, 5.2≤TC<6.2 mmol/L, 3.4≤LDL-C<4.1mmol/L remained significantly associated with the incidence of HTN. Of note, the fifth quintile of RC showed the strongest association with HTN among other lipid parameters, suggesting the strong predictive ability of high RC for HTN risk (fifth quintile of RC: HR 1.68, 95%CI 1.40-2.01, p<0.0001; TG groups: 1.7≤TG<2.3mmol/L: HR 1.29, 95%CI 1.14-1.45, p<0.0001; TG ≥ 2.3 mmol/L: HR 1.36, 95%CI 1.20-1.53, p<0.0001; 5.2≤TC<6.2 mmol/L: HR 1.15, 95%CI 1.04-1.28, p=0.0095; 3.4≤LDL-C<4.1mmol/L: HR 1.18, 95%CI 1.02-1.36, p=0.0274). Kaplan-Meier analysis between RC quintiles and HTN events showed the similar results (Fig.S1).

**Associations between RC, lipid parameters with HTN in subjects with LDL-C < 2.6 mmol/L, HDL-C > 1.0 mmol/L or**
LDL-C < 2.6 mmol/L and HDL-C > 1.0 mmol/L

As shown in Table 4, elevated RC was still significantly associated with the incidence of HTN even if when both LDL-C and HDL-C were well-controlled within ideal range, based on the Chinese guideline for the management of dyslipidemia in adults (when LDL-C <2.6 mmol/L: fifth quintile of RC: HR 1.60, 95%CI 1.24-2.05, p=0.0002; when HDL-C >1.0 mmol/L: fifth quintile of RC: HR 1.71, 95%CI 1.40-2.09, p<0.0001; when LDL-C <2.6 and HDL-C >1.0 mmol/L: fifth quintile of RC: HR 1.69, 95%CI 1.23-2.33, p=0.0040). It is noteworthy that the predictive ability of elevated RC is strongest compared with other lipid parameters even when both LDL-C and HDL-C were both controlled within lower risk ranges.

Associations of RC quintiles with HTN at different levels of age, BMI, fatty liver

Stratified analyses were performed to thoroughly confirm the predictive value of elevated RC for incident HTN shown in Table 5. Multivariate Cox regression analyses found that elevated RC in young subjects (age <55years) was associated with 1.74-fold risk of the development of HTN (HR 1.74, 95%CI 1.40-2.16, p<0.0001). Similar results were observed in all BMI subgroups. To be noted, elevated RC plus underweight (BMI <18.5 kg/m²) group had the highest 2.87-fold risk of HTN (HR 2.87, 95%CI 1.30-6.37, p=0.0464) and the obese subjects with elevated RC had 1.81-fold risk of HTN (HR 1.81, 95%CI 1.11-2.96, p=0.0179). Considering that lipid metabolism is mainly in the liver, stratified analysis was also conducted in fatty liver group to validate the predictive ability of RC for HTN and detect this association whether it is affected by liver function. Multivariate Cox regression model 4 demonstrated that elevated RC still remained associated with HTN both in non-fatty liver and fatty liver groups. Moreover, elevated RC showed a closer association with HTN in fatty liver group than non-fatty liver group, indicating the stronger predictivity of RC for HTN in people with fatty liver (non-fatty liver group: HR 1.46, 95%CI 1.15-1.86, p=0.0021 vs fatty liver group: HR 1.66, 95%CI 1.17-2.36, p=0.0047).

Discussion

This is the first cohort study to confirm the associations of RC, lipid parameters with HTN in the Chinese population. In this large cohort study, we observed that elevated RC was significantly associated with the risk of HTN, even when LDL-C and HDL-C were both well-controlled. Specifically, people in the fifth quintile of RC had a higher risk of HTN than other groups. Although TC, TG and LDL-C were also associated with HTN after adjusting for various confounding factors, the predictive ability of RC for HTN is superior to other lipid parameters, indicating that RC is a superior predictor of HTN. Additionally, subgroups analyses showed a closer association between high RC (in the fifth quintile) and HTN in people with younger age (age<55years), underweight (BMI<18.5 kg/m²) or obesity (BMI>28kg/m²) and fatty liver diseases, and the effect of high RC level on the risk of HTN was more pronounced in such people. Thus, RC could be used as a better predictor for identifying individuals at high risk of developing HTN than other lipid parameters. The findings of our study have significant implications for management of HTN, and indicated targeting RC as important as LDL-C is beneficial of prevention of CVDs.
Dyslipidemia has been regarded as the cornerstone of atherosclerosis and remains as a significant risk factor for CVDs. Though LDL-C has been recommended as a crucial risk factor and therapeutic goal for CVDs in primary prevention, according to ACC/AHA and ESC/EAS guidelines, there is still an alarming number of adverse cardiovascular events regardless of desirable LDL-C lowering therapies. Emerging evidence proposed that RC may play a key role in the residual risk of CVDs. A growing number of literatures suggested that increased RC levels are closely associated with the high risk of atherosclerosis and adverse events of CVDs. But research focusing on the relationship between lipid metabolism and HTN is still lacking, particularly about RC. In a cohort study based on Middle Eastern population, including 2831 non-hypertensive women, TG and TG/HDL were found to be significantly predictive of incident HTN and similar results were obtained from studies on adolescents. More recently, a study of 5173 participants reported that increased RC level was significantly associated with higher central SBP and this association was independent of other lipid levels. The results of our study showed the most significant association of RC with incident HTN, agree with previous studies. Notably, despite LDL-C is the primary therapy target, it is not effectively predictive of HTN in our study. In fact, numerous clinical studies supported the notion that a considerable residual risk of cardiovascular events still exist even when LDL-C is reduced at optimal values. And RC as the cholesterol content of partially lipolyzed TGRLs may be an important contributor of this residual risk to some extent. Clinically, the concentrations of TG serve as a surrogate indicator of TGRLs and RC, which could explain a close association between RC and TG. More recently, genetic and clinical intervention studies reported that RC is valuable in predicting the risk of CVDs and RC as well as TG, but not LDL-C, have been proven to be associated with cardiovascular events. This randomized controlled trial also indicated the stronger predictive ability of RC for cardiovascular events than TG. Our results reached similar conclusions on the association of RC, TG with HTN in the Chinese population. People with TG ≥ 2.3 mmol/L have 1.36-fold risk, and those with increased RC in the fifth quintile have 1.68-fold risk of incident HTN, indicating the higher predictive value of RC for HTN. Also, in hypertensive population, high RC was significantly association with albuminuria that is proven a risk factor for CVDs, and this finding can further support our conclusions. Of note, the association between RC and HTN was more significant in people with obesity (BMI ≥ 28kg/m²) and fatty liver diseases. We speculate that increased adiposity is closely correlated with TGRLs metabolism, contributing to obesity and fatty liver. And adiposity generates an environment where HTN is more likely to develop. Besides, our results provided the evidence concerning the relationship between RC and HTN in the Chinese population. What is more, we firstly investigated RC, traditional lipid parameters and compared their predictive values in this cohort study based on a large Chinese population. Thus, our study proposed that measuring RC clinically to identify individuals at high risk of HTN. It should be emphasized that the management of blood pressure is strengthened for individuals with increased RC, especially in those with fatty liver diseases and obesity.

Another important finding of our present study was that elevated RC consistently expressed as a significant predictor for HTN even when LDL-C and HDL-C were both controlled at appropriate values. In fact, high HDL-C has been considered to be protective of atherosclerosis related to incident HTN, whereas low HDL-C contributed to the increased risk of CVDs. Interestingly, Crosby et al. reported that no causal relationship between low HLD-C and atherosclerosis was observed and it is just an indicator of increased TGRLs.
concentration\textsuperscript{38}. Consistently, our study found that both continuous and categorical RC were negatively associated with HDL-C, but positively related to TG and TC (Table S1), which agree with earlier ones. Theoretically, HDL particles are able to penetrate the media after entering the intima, then leave the arterial wall by the lymphatic vessels and vascular wall of the outer membrane\textsuperscript{39,40}. Conversely, remnants of TGRLs may be too large to penetrate the medium, leading to be trapped in the intima. The activity of LPL at the surface of remnants causes the increased liberation of free fatty acids and foam cells formation, contributing to vascular damage and inflammation\textsuperscript{41}. It might account for the stronger predictive value of HTN; also, environmental and genetic factors can influence the results. Of note, though RC has not been uniform definition, the calculated RC has been confirmed possessing equal credibility of directly RC in predicting CVDs risk in clinical practice\textsuperscript{42}. In view of the convenient and highly cost-effective, RC calculated by the Friedewald formula has been widely promoted to be used in real-world clinical practice.

In summary, in our study, it is first reported RC may be superior to conventional lipid parameters (eg. LDL-C and TG) in predicting the development of HTN in a Chinese population. RC is applied in accurately reflecting the concentrations of TGRLs. In fact, the association of RC with CVDS has been fully demonstrated, and it has a unignored influence on atherosclerotic plaque formation, generating the environment to develop HTN to some extent. Our study revealed the important value of identifying individuals at high risk of developing HTN, who often are neglected due to the targeted LDL-C or HDL-C levels. Taken together, it is of great importance to early monitor RC in clinical practice. More importantly, RC might be both a significant predictor and a new observation or potential target in the management of HTN.

The present study had some limitations. First, RC levels are calculated rather than directly measured. Second, our study only recruited Chinese population, it remains uncertain whether our results could be generalized to other ethnic groups. Finally, though we adjusted for known confounding factors in Cox regression analysis, we cannot deny a possible residual because we did not investigate other medications which might affect this association though this study excluded subjects taking anti-hypertensive drugs.

Conclusions

To conclude, our study was first cohort study and showed that an elevated RC at baseline is independently predictive of development HTN in a Chinese population even when LDL-C or HDL-C was well-controlled at desirable values. More importantly, RC is superior to other lipid parameters in identifying individuals at high risk of incident HTN at an early stage. Therefore, we emphasize the significance of monitoring RC levels in management of HTN in clinical practice and believe RC is a new potential target and efficient biomarker for predicting HTN. We pronounce that targeting increased RC in HTN may contribute to the drug discovery in the field of CVDs and dyslipidemia.

Abbreviations

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase
ASCVD: Atherosclerosis cardiovascular diseases
BMI: Body mass index
CR: Chylomicron remnants
CI: Confidence intervals
CVDs: Cardiovascular diseases
Cr: Creatinine
DBP: Diastolic blood pressure
eGFR: estimated glomerular filtration rate
FPG: Fasting plasma glucose
HDL-C: High-density lipoprotein cholesterol
HTN: Hypertension
HR: Hazard ratios
LDL-C: Low-density lipoprotein cholesterol
IDL: Intermediate density lipoprotein
Lp(a): Lipoprotein(a)
RC: Remnant cholesterol
SBP: Systolic blood pressure
SD: Standard deviations
TC: Total cholesterol
TG: Triglyceride
TGRLs: TG-rich lipoproteins
VLDL: Very low-density lipoprotein

Declarations

Availability of data and materials
The datasets used to support this study are not freely available due to participants’ privacy protection.

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**Competing interests:**

The authors declare no competing interests.

**Consent for publication:**

Not applicable.

**Ethics approval and consent to participate:**

The present study was approved by national and local ethics committees and undertaken in accordance with the Declaration of Helsinki. All participants signed informed consents.

**Authors’ contributions**

Jie Wang, Ying Wang and Guang Wang conceived and designed the study. Jie Wang analyzed and interpreted the data. Yu An and Jia Liu were involved in the collection and interpretation of the data. Jie Wang drafted the article. Song Leng and Guang Wang supervised the study. All authors read and approved the final manuscript.

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Tables

Table 1

Characteristics of study population by RC quintiles
|                  | Total     | RC quantiles | Q1       | Q2       | Q3       | Q4       | Q5       | P-value |
|------------------|-----------|--------------|----------|----------|----------|----------|----------|---------|
| **N**            | 4297      | 4046         | 3711     | 3324     | 3105     |          |          | <0.001  |
| **Age, years**   | 37.00     | 33.00        | 36.00    | 39.00    | 43.00    | 45.00    |          | <0.001  |
|                  | (31.00-48.00) | (29.00-41.00) | (30.00-46.00) | (32.00-49.00) | (34.00-51.00) | (35.00-52.00) |          |         |
| **BMI, kg/m²**   | 23.51     | 21.88        | 22.84    | 23.62    | 24.46    |          |          | <0.001  |
|                  | (21.19-25.90) | (19.96-24.14) | (20.76-25.15) | (21.45-25.96) | (22.27-26.64) | (25.32-27.47) |          |         |
| **SBP, mm/Hg**   | 121.00    | 118.00       | 120.00   | 121.00   | 123.00   |          |          | <0.001  |
|                  | (113.00-130.00) | (110.00-127.00) | (112.00-128.00) | (112.00-130.00) | (114.00-130.00) | (116.00-132.00) |          |         |
| **DBP, mm/Hg**   | 73.00     | 71.00        | 72.00    | 73.00    | 74.00    |          |          | <0.001  |
|                  | (67.00-79.00) | (65.00-77.00) | (66.00-78.00) | (67.00-79.00) | (68.00-80.00) | (70.00-82.00) |          |         |
| **FBG, mmol/L**  | 5.34      | 5.20         | 5.26     | 5.35     | 5.42     |          |          | <0.001  |
|                  | (5.06-5.66) | (4.94-5.46)  | (5.01-5.55) | (5.07-5.66) | (5.15-5.77) | (5.24-5.97) |          |         |
| **TC, mmol/L**   | 4.72      | 4.05         | 4.49     | 4.82     | 5.17     |          |          | <0.001  |
|                  | (4.19-5.34) | (3.67-4.45)  | (4.12-4.90) | (4.39-5.25) | (4.73-5.67) | (5.09-6.25) |          |         |
| **TG, mmol/L**   | 1.39      | 0.98         | 1.21     | 1.42     | 1.76     |          |          | <0.001  |
|                  | (0.98-1.95) | (0.76-1.30)  | (0.90-1.55) | (1.07-1.82) | (1.32-2.21) | (1.85-3.47) |          |         |
| **HDL-C, mmol/L**| 1.30      | 1.42         | 1.37     | 1.28     | 1.21     |          |          | <0.001  |
|                  | (1.09-1.53) | (1.23-1.63)  | (1.17-1.61) | (1.09-1.51) | (1.04-1.46) | (0.93-1.31) |          |         |
| **LDL-C, mmol/L**| 2.48      | 2.06         | 2.35     | 2.58     | 2.80     |          |          | <0.001  |
|                  | (2.06-2.95) | (1.73-2.42)  | (2.01-2.72) | (2.22-2.97) | (2.42-3.19) | (2.43-3.41) |          |         |
| **ALT, mmol/L**  | 18.83     | 14.80        | 16.67    | 18.92    | 21.36    |          |          | <0.001  |
|                  | (13.44-27.85) | (11.20-20.37) | (12.17-24.10) | (14.00-26.61) | (15.66-31.13) | (18.00-38.71) |          |         |
| **AST, mmol/L**  | 19.71     | 17.92        | 19.00    | 19.85    | 20.75    |          |          | <0.001  |
|                  | (16.78-23.72) | (15.48-21.00) | (16.06-22.51) | (17.00-23.56) | (17.59-24.95) | (18.64-27.00) |          |         |
| **eGFR, mL/min·1.73 m²** | 92.90    | 96.78        | 94.50    | 91.82    | 90.32    |          |          | <0.001  |
|                  | (82.55-104.49) | (86.01-108.25) | (83.91-106.23) | (81.71-103.64) | (80.61-101.14) | (79.53-100.27) |          |         |
| **RC, mmol/L**   | 0.85      | 0.55         | 0.73     | 0.90     | 1.10     |          |          | <0.001  |
|                  | (0.67-1.11) | (0.47-0.60)  | (0.70-0.78) | (0.85-0.94) | (1.04-1.16) | (1.34-1.73) |          |         |
| **SEX, %**       |          |              |          |          |          |          |          | <0.001  |
Data were mean ± SD or median (Q1-Q3) for skewed variables or numbers (proportions) for categorical variables.

HTN hypertension, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, FBG fasting plasma glucose, ALT alanine transferase, AST aspartate transferase, GGT gamma-glutamyl transferase, TG triglyceride, TC high cholesterol, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, eGFR estimated glomerular filtration rate.

### Table 2

Univariate analysis based on Cox model
| Variables     | Statistics   | HR (95% CI)     | P-value  |
|---------------|--------------|-----------------|----------|
| Age, years    | 39.85 ± 11.44| 1.05 (1.05, 1.05)| <0.0001 |
| BMI, kg/m²    | 23.28 ± 5.47 | 1.02 (1.02, 1.02)| <0.0001 |
| ALT, U/L      | 24.46 ± 25.37| 1.00 (1.00, 1.00)| <0.0001 |
| AST, U/L      | 21.71 ± 12.55| 1.00 (1.00, 1.01)| <0.0001 |
| GGT, U/L      | 24.01 ± 24.52| 1.01 (1.01, 1.01)| <0.0001 |
| RC, mmol/L    | 0.94 ± 0.46  | 1.40 (1.34, 1.45)| <0.0001 |
| TC, mmol/L    | 4.81 ± 0.90  | 1.27 (1.22, 1.33)| <0.0001 |
| TG, mmol/L    | 1.62 ± 1.12  | 1.13 (1.12, 1.15)| <0.0001 |
| HDL-C, mmol/L | 1.33 ± 0.34  | 0.42 (0.36, 0.49)| <0.0001 |
| LDL-C, mmol/L | 2.53 ± 0.67  | 1.36 (1.28, 1.45)| <0.0001 |
| FBG, mmol/L   | 5.50 ± 1.02  | 1.21 (1.18, 1.23)| <0.0001 |

Table 3

Association of RC, lipid parameters with HTN in total subjects
| Variable | Non-adjusted | Adjust 1 | Adjust 2 | Adjust 3 | Adjust 4 |
|----------|--------------|----------|----------|----------|----------|
|          | HR (95%CI) P-value | HR (95%CI) P-value | HR (95%CI) P-value | HR (95%CI) P-value | HR (95%CI) P-value |
| RC, mmol/L | 1.40 (1.34, 1.45) <0.0001 | 1.30 (1.22, 1.39) <0.0001 | 1.20 (1.11, 1.30) <0.0001 | 1.17 (1.08, 1.26) 0.0001 | 1.15 (1.06, 1.24) 0.0006 |
| RC quantiles | | | | | |
| Q1 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Q2 | 1.73 (1.46, 2.07) <0.0001 | 1.46 (1.22, 1.74) <0.0001 | 1.41 (1.17, 1.70) 0.0003 | 1.40 (1.16, 1.69) 0.0004 | 1.37 (1.14, 1.65) 0.0010 |
| Q3 | 2.07 (1.74, 2.45) <0.0001 | 1.49 (1.25, 1.77) <0.0001 | 1.40 (1.16, 1.68) 0.0003 | 1.39 (1.16, 1.67) 0.0004 | 1.36 (1.13, 1.63) 0.0010 |
| Q4 | 2.53 (2.14, 3.00) <0.0001 | 1.65 (1.39, 1.96) <0.0001 | 1.54 (1.29, 1.85) <0.0001 | 1.53 (1.28, 1.83) <0.0001 | 1.49 (1.24, 1.78) <0.0001 |
| Q5 | 3.52 (2.99, 4.15) <0.0001 | 2.09 (1.77, 2.46) <0.0001 | 1.79 (1.50, 2.14) <0.0001 | 1.74 (1.45, 2.08) <0.0001 | 1.68 (1.40, 2.01) <0.0001 |
| TC, mmol/L | 1.27 (1.22, 1.33) <0.0001 | 1.14 (1.09, 1.20) <0.0001 | 1.10 (1.04, 1.16) <0.0001 | 1.09 (1.04, 1.15) <0.0001 | 1.09 (1.04, 1.15) <0.0006 |
| TC categorical | | | | | |
| <5.2 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| >=5.2, <6.2 | 1.46 (1.32, 1.62) <0.0001 | 1.21 (1.09, 1.34) 0.0004 | 1.15 (1.03, 1.28) 0.0104 | 1.15 (1.03, 1.28) 0.0110 | 1.15 (1.04, 1.28) 0.0095 |
| >=6.2 | 1.74 (1.49, 2.03) <0.0001 | 1.29 (1.10, 1.51) 0.0017 | 1.15 (0.98, 1.36) 0.0931 | 1.15 (0.97, 1.35) 0.1034 | 1.15 (0.98, 1.36) 0.0915 |
| TG, mmol/L | 1.13 (1.12, 1.15) <0.0001 | 1.10 (1.08, 1.13) <0.0001 | 1.08 (1.05, 1.11) <0.0001 | 1.07 (1.04, 1.10) <0.0001 | 1.06 (1.03, 1.09) <0.0001 |
| TG categorical | | | | | |
| <1.7 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| >=1.7, <2.3 | 1.81 (1.62, 2.03) <0.0001 | 1.41 (1.26, 1.58) <0.0001 | 1.33 (1.18, 1.50) <0.0001 | 1.33 (1.18, 1.49) <0.0001 | 1.29 (1.14, 1.45) <0.0001 |
| >=2.3 | 2.33 (2.09, 2.61) <0.0001 | 1.66 (1.48, 1.85) <0.0001 | 1.44 (1.28, 1.63) <0.0001 | 1.40 (1.24, 1.58) <0.0001 | 1.36 (1.20, 1.53) <0.0001 |
| HDL-C, mmol/L | 0.42 (0.36, 0.49) <0.0001 | 0.66 (0.56, 0.77) <0.0001 | 0.75 (0.63, 0.89) 0.0007 | 0.77 (0.65, 0.92) 0.0027 | 0.84 (0.71, 0.99) 0.0373 |
| HDL categorical | | | | | |
| >=1 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
|                  | <1          | 1.67 (1.50, 1.86) <0.0001 | 1.28 (1.14, 1.43) <0.0001 | 1.16 (1.03, 1.30) 0.0149 | 1.13 (1.00, 1.27) 0.0420 | 1.10 (0.97, 1.23) 0.1359 |
|-----------------|-------------|--------------------------|---------------------------|--------------------------|--------------------------|--------------------------|
| LDL-C, mmol/L   | 1.36 (1.28, 1.45) <0.0001 | 1.14 (1.06, 1.21) 0.0001  | 1.10 (1.03, 1.18) 0.0044  | 1.11 (1.03, 1.19) 0.0033  | 1.10 (1.03, 1.18) 0.0044  |                         |
| LDL categorical | <34         | 1.0                      | 1.0                       | 1.0                      | 1.0                      | 1.0                      |
|                 | >=3.4, <4.1 | 1.57 (1.37, 1.81) <0.0001 | 1.24 (1.08, 1.43) 0.0023  | 1.18 (1.02, 1.36) 0.0256  | 1.17 (1.02, 1.35) 0.0299  | 1.18 (1.02, 1.36) 0.0274  |
|                 | >=4.1       | 1.33 (0.98, 1.79) 0.0646  | 1.06 (0.78, 1.42) 0.7227  | 0.93 (0.68, 1.27) 0.6323  | 0.94 (0.69, 1.28) 0.6948  | 0.93 (0.68, 1.27) 0.6391  |

Model 0: Adjusted for no confounding factors  
Model 1: Adjusted for age and sex  
Model 2: Adjusted for age; sex; BMI; ALT; AST; eGFR  
Model 3: Adjusted for age; sex; BMI; ALT; AST; eGFR; FBG  
Model 4: Adjusted for age; sex; BMI; ALT; AST; eGFR; FBG; smoking habits; drinking habits

Figures
Figure 1

Flow chart of the selection study participants

Supplementary Files

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