Remnant Cholesterol and Ischemic Cardiovascular Disease: A Cross-Sectional Study in Northern China

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Research Article

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Abstract

Background:

Heterogeneity exists in the relationship of remnant cholesterol (RC) with cardiovascular disease. In this study, we examined the association between RC and ischemic cardiovascular disease (ICVD) risks and the RC-related risk beyond low-density lipoprotein cholesterol (LDL-C) among people in northern China.

Methods:

We determined the lipid profile among 65,236 people aged 35–75 years, enrolled between 2015 and 2017, who lived in Inner Mongolia for more than 6 months. Adjusted logistic regression models were used to assess the associations between RC concentration and ICVD risks.

Results:

In total, 2350 ICVD events were included in the study. RC was significantly associated with the risk of ICVD, CHD events, and ischemic stroke (IS) (ICVD odds ratio [OR] fourth quartile vs first quartile (Q4 vs Q1) 1.253, 95% confidence interval [CI] 1.104–1.421, \( P_{\text{trend}} < 0.001 \); CHD events \( \text{OR}_{\text{Q4 vs Q1}} 1.222, 95\% \text{ CI} 1.018–1.466, P_{\text{trend}} = 0.034 \); IS \( \text{OR}_{\text{Q4 vs Q1}} 1.288, 95\% \text{ CI} 1.090–1.522, P_{\text{trend}} = 0.001 \)). This association remained significant after including LDL-C and high-density lipoprotein cholesterol (HDL-C). Moreover, the discordant high RC/low LDL-C group was associated with increased ICVD risk compared with the low RC/low LDL-C group (OR 1.174, 95% CI 1.029–1.339). Similar results were obtained when adjusting for traditional risk factors of ICVD.

Conclusions:

We found that RC was associated with an increased risk of ICVD independent of traditional risk factors, LDL-C, and HDL-C levels. The interaction of RC and LDL-C was associated with the risk of ICVD risks.

Background

Cardiovascular disease (CVD) has the highest death rate in the world[1]. CVD is also the main cause of death and premature death in China[2, 3], with the disease accounting for more than 40% of deaths[4]. In China, the prevalence of CVD is “high in the north and low in the south”[5]. Plasma lipids, especially elevated low-density lipoprotein cholesterol (LDL-C), are a risk factor for CVD[6]. Moreover, a considerable residual risk remains after achieving recommended LDL-C targets[7-11]. Therefore, LDL-C and conventional lipid profiles cannot explain all CVD risk. Studies have shown that the above residual risk can be partly attributed to remnant cholesterol (RC)[12, 13].

Mounting evidence from epidemiologic studies has established that RC is associated with the onset and recurrence of CVD[14-17]. Quispe et al. reported that RC was associated with the risk of CVD, and this
association was independent of traditional cardiovascular risk factors, LDL-C, and apolipoprotein B levels\cite{18}. A heart study conducted in urban Copenhagen also showed that with increased non-fasting RC, the risk of ischemic heart disease (IHD), myocardial infarction, and all-cause death gradually increased\cite{19}. Varbo et al. found values of non-fasting RC increased by 1 mmol/L (39 mg/dL) and an increased risk of IHD by 2.8 times in Multiple studies from Copenhagen\cite{15}. Recently, the results of a nested case-control study from China Kadoorie Biobank showed that increased RC concentrations increase the risk of myocardial infarction and ischemic stroke (IS)\cite{20}.

The evidence related to the risk of RC and CVD is mostly from Western countries, However, little information is available in China, especially northern China, among people with specific eating behaviors and environments. Inner Mongolia is representative of northern China owing to high similarity in behavioral, environmental, population, and regional characteristics. The prevalence of high-risk populations for CVD in northern China is elevated, and the treatment control rate is low\cite{21}. Dyslipidemia is an important risk factor threatening the health of people in this area\cite{22}. Therefore, investigating the relationship between RC and CVD is of great importance for the prevention of CVD in northern China. In this study, we aimed to investigate the association between RC and ICVD, independent of LDL-C, in a large cross-sectional study. Our findings can provide new evidence for the prevention of CVD in northern China.

**Methods**

**Study design**

Participants in our study were recruited from the "Early screening and comprehensive intervention project for high-risk groups of CVD" in Inner Mongolia. During 2015–2017, multistage stratified cluster sampling method was used to recruit the study population. In the first stage, six cities (Hohhot, Wuhai, Chifeng, Erdos, Hulun Buir, and Xingan League) were randomly selected from Inner Mongolia province, based on geographic, economic, and ethnic distribution factors. In the second stage, we selected one district or county from each of these cities according to the size of the district or county and population stability. In the third stage, two or three urban residential communities or rural villages were selected from each district or county, according to the size of communities or villages.

This study was approved by the ethics committee of Inner Mongolia Medical University (YKD202101133) and all enrolled participants provided their written informed consent. A total of 70,380 participants in the province of Inner Mongolia were finally enrolled.

**Study participants**

Residents aged 35–75 years who had lived in Inner Mongolia for more than 6 months from 2015 to 2017 were included in the study. We excluded patients with malignant neoplasms and other diseases (hemorrhagic stroke, chronic obstructive pulmonary disease) that might influence the association between RC and ICVD. A total of 65,236 participants were finally included in the study.
Data collection

Field investigation included a questionnaire survey, physical examination, and biochemical examination. In-person interviews were conducted by trained investigators using a standardized questionnaire. We collected information on social demographic characteristics such as age, ethnic group, disease history, medication history, and lifestyle factors including smoking. Data of height, weight, and blood pressure were obtained in physical examination.

Two consecutive blood pressure measurements were taken and the mean blood pressure value of the two readings was used. For each participant, blood pressure measurement was performed on the right upper arm after 5 minutes of rest, with the participant in a seated position, using an electronic sphygmomanometer (Omron HEM-7430). Fasting blood samples were collected after at least 10 hours of overnight fasting. Venous blood specimens were collected in Vacutainer tubes containing ethylenediaminetetraacetic acid. Serum total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were measured using an automatic biochemical analyzer (Cardiochek PA). All laboratory equipment was calibrated.

Definitions of variables

Current smoker was defined as smoking at least one cigarette per day in the past 12 months. body mass index (BMI) was calculated as weight in kilograms divided by height squared, in meters, and obesity was defined as BMI ≥ 28 kg/m². Patients with diabetes were defined as those who self-reported diabetes, those taking hypoglycemic agents, those receiving insulin injections, or those with measured fasting plasma glucose level ≥ 7.0 mmol/L. Hypertension was defined as an average systolic blood pressure (SBP) of at least 140 mmHg or an average diastolic blood pressure (DBP) of at least 90 mmHg, or self-reported use of antihypertensive medication in the past 2 weeks. Of patients with dyslipidemia, those who reported taking lipid-lowering medications (including Western medicine, Chinese patent medicine, and traditional Chinese medicine) during the previous 2 weeks were considered to be treated for dyslipidemia. Calculated RC was TC minus HDL-C and LDL-C, as previously reported[23].

A history of ICVD was defined as any self-reported history of coronary heart disease (CHD) events (including myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention) and IS.

Discordance definition

There is no physiological cut-point for discordance among different lipid or lipoprotein measures. Therefore, we defined discordance using clinical cut-points of LDL-C (2.6 and 3.4 mmol/L, respectively) and quartiles of RC. The population was divided into: (i) LDL-C ≤ clinical cut-point and RC ≤ one of the quartiles (concordant low RC), (ii) LDL-C ≤ clinical cut-point but RC > one of the quartiles (discordantly high RC), (iii) LDL-C > clinical cut-point but RC ≤ one of the quartiles (discordantly low RC), and (iii) LDL-
C > clinical cut-point but RC > one of the quartiles (concordant high RC). We used several cut-points to define discordance and to assess the robustness of our findings.

**Statistical analyses**

Numerical variables with a normal distribution are expressed using mean ± standard deviation; otherwise, variables are described using median and interquartile range. Categorical variable data are described using percentage. Differences between the baseline characteristics of ICVD and non-ICVD were compared with the chi-square and Mann–Whitney U tests. We constructed logistic regression models to assess the association between RC levels (given a non-normal distribution) and the risk of ICVD (including CHD events and IS). Model 1 was adjusted by age and sex; Model 2 was additionally adjusted for smoking, obesity, hypertension, diabetes, and use of lipid-lowering therapy. To further explore the interaction between LDL-C and RC in ICVD, the odds ratios (ORs) and 95% confidence intervals (CIs) of different combinations of LDL-C and RC and ICVD were calculated using the same models. A two-sided significance level was set at \( P < 0.05 \). We used SAS version 9.4 for all statistical analyses (SAS Institute Inc., Cary, NC, USA).

**Results**

Characteristics of study participants are presented in Table 1. This study included 65,236 participants (including 2350 patients with ICVD). The mean participant age was 54 years, 58.6% were women, and 89.9% were Han nationality. The median RC level among participants was 0.60 mmol/L. Compared with patients without ICVD, those with ICVD were more like to be male (50.9% vs. 41.0%), older (median: 60 vs. 54 years), more likely to have a higher prevalence of hypertension (72.4% vs. 54.9%) and diabetes (28.0% vs. 18.8%), and more likely to use more lipid-lowering therapy (14.5% vs. 1.9%). Patients with ICVD had slightly higher TG and lower HDL-C levels than those without ICVD. Higher RC levels were more common in patients with ICVD; the median RC was 0.64 mmol/L and 0.60 mmol/L in participants with and without ICVD.

Table 1 Baseline characteristics of study participants, by group
<table>
<thead>
<tr>
<th></th>
<th>ICVD n=2350</th>
<th>non-ICVD n=62886</th>
<th>total n=65236</th>
<th>χ²/Z</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, year (M P&lt;sub&gt;25&lt;/sub&gt;, P&lt;sub&gt;75&lt;/sub&gt;)</td>
<td>60±54.66</td>
<td>54±47.61</td>
<td>54±47.62</td>
<td>-27.452</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90.713</td>
</tr>
<tr>
<td>Female</td>
<td>1155(49.1)</td>
<td>37105(59.0)</td>
<td>38260(58.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>1195(50.9)</td>
<td>25781(41.0)</td>
<td>26976(41.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic group, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>5.762</td>
<td>0.056</td>
</tr>
<tr>
<td>Han</td>
<td>2148(91.4)</td>
<td>56527(89.9)</td>
<td>58675(89.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mongol</td>
<td>170(7.2)</td>
<td>5364(8.5)</td>
<td>5534(8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other minority</td>
<td>32±1.4</td>
<td>995±1.6</td>
<td>1027±1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt; (M P&lt;sub&gt;25&lt;/sub&gt;, P&lt;sub&gt;75&lt;/sub&gt;)</td>
<td>26.1±23.7, 28.4</td>
<td>25.6±23.3, 28.0</td>
<td>25.6±23.3, 28.0</td>
<td>-5.018</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>676±28.8</td>
<td>15693±25.0</td>
<td>16369±25.1</td>
<td>17.507</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>580(24.7)</td>
<td>15513(24.7)</td>
<td>16093(24.7)</td>
<td>0.000</td>
<td>0.989</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1701(72.4)</td>
<td>34553(54.9)</td>
<td>36254(55.6)</td>
<td>278.994</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>658(28.0)</td>
<td>11794(18.8)</td>
<td>12452(19.1)</td>
<td>125.378</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>lipid-lowering therapy, n (%)</td>
<td>341±14.5</td>
<td>1194±1.9</td>
<td>1535±2.4</td>
<td>1562.267</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Blood lipid parameters (M P&lt;sub&gt;25&lt;/sub&gt;, P&lt;sub&gt;75&lt;/sub&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.46(3.70, 5.15)</td>
<td>4.48(3.90, 5.14)</td>
<td>4.48(3.89, 5.14)</td>
<td>-4.034</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.40(1.02, 1.97)</td>
<td>1.31(0.97, 1.85)</td>
<td>1.31(0.97, 1.86)</td>
<td>-6.111</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.27(1.05, 1.54)</td>
<td>1.37(1.13, 1.66)</td>
<td>1.37(1.13, 1.66)</td>
<td>-11.871</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.39(1.77, 3.01)</td>
<td>2.40(1.90, 2.95)</td>
<td>2.40(1.90, 2.96)</td>
<td>-2.161</td>
<td>0.031*</td>
</tr>
<tr>
<td>RC, mmol/L</td>
<td>0.64(0.46, 0.91)</td>
<td>0.60(0.43, 0.86)</td>
<td>0.60(0.43, 0.86)</td>
<td>-6.614</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Blood pressure parameters (M P&lt;sub&gt;25&lt;/sub&gt;, P&lt;sub&gt;75&lt;/sub&gt;)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SBP, mmHg  
143.5(130.5,158.5)  
137.5 (125.5,153.0)  
137.5 (125.5,153.0)  
-12.592  
<0.001*

DBP, mmHg  
85.5(78.0,93.0)  
84.0(77.0,91.5)  
84.0(77.0,92.0)  
-5.029  
<0.001*

Results are expressed as median with interquartile range or n (%),

* Significant difference.

Abbreviations: ICVD, ischemic cardiovascular disease; BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

The risk of ICVD was very high in the higher level of RC whether RC is analyzed as a continuous variable(Figure S1) or a categorical variable(Figure S2). The risk of ICVD was very high in the upper quartile groups of RC concentration compared with the lowest quartile group, after adjusting for traditional cardiovascular risk factors. The ORs of the highest quartile group were 1.243 (95% CI 1.095–1.412) and 1.154 (95% CI 1.014–1.314) after including LDL-C and HDL-C, respectively (Figure 1). Similar results were obtained when stratified by other risk factors(Figure S3).

The risk of CHD and IS was significantly increased across quartiles of RC after adjusting for traditional cardiovascular risk factors. Compared with the lowest quartile group of RC, the highest quartile group of RC was still associated with the risk of CHD (OR 1.229, 95% CI 1.02–1.476) and IS (OR 1.267, 95% CI 1.072–1.499) when adjusting for LDL-C(Figure 2, Figure 3).

To further study the role of RC in the residual risk of ICVD beyond LDL-C, participants were divided into four groups according to different combinations of LDL-C and RC. Compared with the concordant low RC and LDL-C group, the ICVD risk in the high RC and low LDL-C group showed a significant increase, after adjusting for sex and age or adding traditional cardiovascular risk factors. However, the ICVD risk in the low RC and high LDL-C group was similar to that of the concordant low RC and LDL-C group (Table 2).

Table 2 Odds ratios (95% confidence intervals) for ischemic cardiovascular disease across LDL-C vs. remnant cholesterol concordant/discordant groups by LDL-C clinical cut-points (2.6 and 3.4 mmol/L, respectively) and quartile equivalents for remnant cholesterol
<table>
<thead>
<tr>
<th>Lipid groups</th>
<th>RC</th>
<th>n CVD events/n individuals</th>
<th>Model 1,OR(95% CI)</th>
<th>Model 2,OR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutpoints:LDL-C 2.6mmol/L;RC 0.43mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=39506)</td>
<td>≤cutpoint</td>
<td>319/11501</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>1064/28005</td>
<td>1.366(1.202-1.553)*</td>
<td>1.174(1.029-1.339)*</td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=25761)</td>
<td>≤cutpoint</td>
<td>148/4609</td>
<td>1.101(0.902-1.343)</td>
<td>1.126(0.921-1.377)</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>820/21152</td>
<td>1.311(1.147-1.498)*</td>
<td>1.245(1.085-1.427)*</td>
</tr>
<tr>
<td>Cutpoints:LDL-C 2.6mmol/L;RC 0.6mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=39506)</td>
<td>≤cutpoint</td>
<td>677/21672</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>706/17834</td>
<td>1.302(1.168-1.451)*</td>
<td>1.121(1.002-1.254)*</td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=25761)</td>
<td>≤cutpoint</td>
<td>362/11078</td>
<td>0.994(0.872-1.133)</td>
<td>1.036(0.907-1.182)</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>606/14683</td>
<td>1.264(1.127-1.416)*</td>
<td>1.230(1.094-1.383)*</td>
</tr>
<tr>
<td>Cutpoints:LDL-C 2.6mmol/L;RC 0.86mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=39506)</td>
<td>≤cutpoint</td>
<td>1020/30261</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>363/9245</td>
<td>1.224(1.082-1.384)*</td>
<td>1.087(0.958-1.234)</td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=25761)</td>
<td>≤cutpoint</td>
<td>648/18704</td>
<td>0.972(0.878-1.076)</td>
<td>1.041(0.939-1.155)</td>
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<tr>
<td></td>
<td>≤cutpoint</td>
<td>320/7057</td>
<td>1.301(1.142-1.482)*</td>
<td>1.278(1.118-1.461)*</td>
</tr>
<tr>
<td>Cutpoints:LDL-C 3.4mmol/L;RC 0.43mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=57384)</td>
<td>≤cutpoint</td>
<td>424/14936</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>1602/42448</td>
<td>1.318(1.181-1.471)*</td>
<td>1.163(1.039-1.303)*</td>
</tr>
<tr>
<td>LDL-C≤cutpoint(n=7883)</td>
<td>≤cutpoint</td>
<td>43/1174</td>
<td>1.237(0.897-1.706)</td>
<td>1.220(0.882-1.687)</td>
</tr>
<tr>
<td></td>
<td>≤cutpoint</td>
<td>282/6709</td>
<td>1.384(1.183-1.618)*</td>
<td>1.292(1.101-1.515)*</td>
</tr>
</tbody>
</table>
Discussion

The increasing burden of CVD in China has become a major public health problem. According to the Summary of China Cardiovascular Health and Disease Report 2019[24], the prevalence and mortality of CVD in China are still on the rise. CVD deaths are the leading cause of total deaths among urban and rural residents, that is, two of every five deaths are owing to CVD. As a region that is representative of northern China, the prevalence of high-risk groups for CVD in Inner Mongolia is elevated, but the treatment and control rates are low[22, 25]. High LDL-C is recognized as an important risk factor for CVD, but increasing evidence shows that residual risk remains even if LDL-C returns to normal levels. Therefore, the use of updated blood lipid indicators for cardiovascular disease risk stratification is particularly important for the primary prevention of CVD in northern China. In our large-scale cross-sectional study in Inner Mongolia, we comprehensively evaluated the association between RC and ICVD in Inner Mongolia. The results showed that high levels of RC were related to the risk of ICVD, apart from traditional cardiovascular risk factors including demographic factors (age and sex), lifestyle risk factors (smoking,
obesity), chronic disease (hypertension, diabetes), and lipid-lowering therapy. Our results confirm previous evidence regarding the relationship between RC and ICVD in the general population.

The cholesterol content of triglyceride-rich lipoproteins (TRLs) is usually referred to as RC, which includes very low- and intermediate-density lipoproteins in the fasting state and chylomicron remnants in the non-fasting state. Studies have shown that RC can increase the risk of morbidity, recurrence, and death owing to ICVD\cite{17,18,26}. Castañer et al. followed high-risk groups in Spain for 4.8 years. They found that in overweight or obese individuals with high cardiovascular risk, independent of other risk factors, high RC levels were associated with the risk of cardiovascular adverse events (myocardial infarction, stroke, cardiovascular disease death)\cite{17}. A Danish cohort study showed that among patients diagnosed with myocardial infarction and IS, RC was decreased to 0.8 mmol/L and 2.1 mmol/L and the incidence of major adverse cardiovascular events was decreased by 20% and 50%, respectively\cite{16}. Previous studies have shown that after adjusting for major cardiovascular risk factors, fasting RC levels are strongly correlated with CHD events\cite{27,28}. Epidemiological studies have shown that RC is associated with the risk of myocardial infarction\cite{23,29-31}. In the Women’s Health Study cohort in the United States, high RC levels are associated with the risk of myocardial infarction. Compared with the first quartile, the fourth quartile OR was 3.05 (95% CI 1.46–6.39). This association remained significant after adjusting for LDL-C\cite{30}. RC is associated with the risk of IS\cite{32} and has predictive value for the incidence of IS\cite{33}. The results of a 14-year Copenhagen study followed a population without cardiovascular disease at baseline and showed that a gradual increase of RC level was associated with a gradual increase in the risk of IS\cite{34}. Similar results were found in our study, with participants who had higher RC levels tending to have a higher risk of ICVD, after adjusting for traditional cardiovascular risk factors and LDL-C.

In our study, the association between high RC level and ICVD risk remained statistically significant after adjusting for LDL-C level. We further explored the association between different combinations of RC and LDL-C and risk of ICVD. In this study, higher RC concentrations (three RC cut-points: >0.43 mmol/L, >0.60 mmol/L, >0.86 mmol/L) were still associated with a higher risk of ICVD, regardless of whether LDL-C concentrations. The highest risk was found in patients with higher concentrations of both RC and LDL-C. These results suggest that RC is associated with a residual risk for ICVD beyond LDL-C. These findings are basically consistent with relevant research results in China and other countries\cite{17,27,28,30}. Prospective cohort studies have also shown that RC levels are positively correlated with CHD events, but this correlation disappears after adjusting for other lipid variables, such as TG, LDL-C, and HDL-C\cite{26,35}. These conflicting data are mainly derived from populations in the United States. The conclusions for Chinese populations remain unclear owing to limited studies.

Mechanistically, the most likely explanation behind the association between high RC concentrations and increased risk for ICVD is that the cholesterol content of remnant particles contributes not only to atherosclerotic plaque formation but also to local inflammation. A high concentration of RC in serum would contribute to increased penetration into the arterial wall, where RC is more easily trapped and taken
up by macrophages than LDL-C, which leads to faster formation of foam cells\cite{36}. Additionally, in atherogenic dyslipidemia, TRLs are more abundant, larger, and carry more cholesterol than LDL; thus, it is not surprising that their RC content has been associated with ICVD risk in population-based observational studies. However, RC from the hydrolysis of TRLs could also induce the production of inflammation-associated cytokines, which may lead to ICVD severity\cite{14}.

There are some limitations in this study. First, owing to the cross-sectional observational study design, we cannot determine a causal relationship between RC and ICVD, despite adjustment for traditional risk factors of ICVD and a large sample. Second, indirect calculation of RC in our study might lead to underestimation of its value in comparison with direct measurement\cite{23}. However, the indirect calculation of RC is an inexpensive method that can provide valuable data for clinical management of ICVD.

**Conclusions**

Our study further confirmed that RC is an independent risk factor for ICVD, apart from other CVD risk factors, especially LDL-C and HDL-C levels. Our findings suggested that RC should be considered for use as an additional primary prevention target alongside LDL-C.

**Abbreviations**

RC: remnant cholesterol; ICVD: ischemic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CHD: coronary heart disease; IS: ischemic stroke; HDL-C: high-density lipoprotein cholesterol; IHD: ischemic heart disease; TC: total cholesterol; TG: triglyceride; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TRLs: triglyceride-rich lipoproteins; OR: odds ratio; CI: Confidence interval

**Declarations**

**Acknowledgment**

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**Authors’ contributions**

W. Z., Y. B., Z. T., Y. M. and J. W. analyzed and interpreted the data. M. L. and N. Z. wrote the manuscript. H. B., T. Y., H. Z. and Y. Z. supervised and modified statistical analysis. X. Z., X. F. participated in the study concept and design, revising it critically for important intellectual content and final approval of the published version. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed in the current study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

The manuscript or parts of it were not published or submitted elsewhere. This study was approved by the ethics committee of Inner Mongolia Medical University (YKD202101133) and all enrolled participants provided their written informed consent.

Consent for publication

All authors have read and approved the content, and they agree to submit it for consideration for publication in the journal.

Competing interests

The authors have no competing interests.

Supplemental Material

Tables S1–S3

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**Figures**
Figure 1

Figure 2

Logistic regression analysis of the relationship between remnant cholesterol and coronary heart disease events Model 1: adjusted for sex and age. Model 2: Model 1 plus adjustment for current smoker, obesity, hypertension, diabetes, lipid-lowering therapy. Model 3: Model 2 plus adjustment for low-density lipoprotein cholesterol. Model 4: Model 2 plus adjustment for high-density lipoprotein cholesterol. RC, remnant cholesterol; OR, odds ratio; CI, confidence interval.
Figure 3


Supplementary Files

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- Supplementarymaterial.docx