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ORIGINAL RESEARCH

Joint Association of Remnant Cholesterol and Body Mass Index with Hypertension: A National Cohort Study in Chinese Adults

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Background: Hypertension, a major global health concern, is closely associated with obesity and lipid abnormalities. Remnant cholesterol (RC), a triglyceride-rich lipoprotein component, has been linked to cardiovascular diseases, but its joint impact with body mass index (BMI) on hypertension risk remains unclear.

Methods: We analyzed data from 3805 participants (mean age: 57 years; 44.3% male) in the China Health and Retirement Longitudinal Study (CHARLS) from 2011–2020. Inclusion criteria were adults aged over 45 years with complete data on blood lipids and BMI. Participants with baseline hypertension or missing covariate data were excluded. Cox proportional hazard models assessed associations, while mediation analysis explored RC's role in BMI-hypertension linkage.

Results: Over a 9-year follow-up, 590 participants developed hypertension. Obesity (BMI ≥28.0 kg/m²) and high RC levels were independently associated with hypertension (HR: 2.18; 95% CI: 1.48–3.21 for the highest RC tertile). RC mediated 7.07% of BMI's effect on hypertension, and BMI mediated 29.3% of RC's effect.

Conclusion: This study highlights the intertwined roles of BMI and RC in hypertension development. Targeting both risk factors may enhance prevention strategies.

Keywords: CHARLS, hypertension, BMI, remnant cholesterol, mediating effect

Introduction

Hypertension remains a leading cause of global morbidity and mortality, contributing significantly to cardiovascular disease (CVD) and other chronic conditions such as stroke, heart failure, and renal impairment.[1] The identification and management of modifiable risk factors, including obesity and lipid abnormalities, have been central to the prevention of hypertension and its complications.[2] Among the lipid markers, remnant cholesterol (RC), which represents the cholesterol content in triglyceride-rich lipoproteins, has gained attention due to its strong association with cardiovascular events.[3,4] Unlike low-density lipoprotein cholesterol (LDL-C), which has been extensively studied, RC has emerged as a potential independent risk factor for atherosclerotic cardiovascular diseases and metabolic disturbances.[5,6]

Body mass index (BMI), an established marker of adiposity, has been directly linked with the development of hypertension, particularly through its effects on metabolic and inflammatory pathways. Individuals with elevated BMI are more likely to exhibit insulin resistance, dyslipidemia, and systemic inflammation,[7] all of which contribute to the pathogenesis of hypertension. Despite the clear connection between BMI and hypertension, the precise role of lipid abnormalities, specifically RC, in mediating this relationship is not well understood.

Recent studies suggest that elevated RC levels may exacerbate the risk of hypertension, particularly in individuals with increased adiposity.[8,9] Guo et al and Shi et al have indicated that elevated RC emerged as an independent risk factor

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of incident hypertension.[8,10] The accumulation of RC is thought to promote endothelial dysfunction, inflammatory processes and insulin resistance, further elevating blood pressure in susceptible individuals.[11–13] Liu et al reported that RC and TG levels exhibited a stronger association with arterial stiffness, assessed by brachial-ankle pulse wave velocity, compared to other lipid markers.[14] Additionally, another study identified RC as an independent predictor of endothelial dysfunction, as indicated by flow-mediated vasodilation, in the general population.[15]

However, most studies have focused on a single risk factor, either lipid abnormalities or obesity, without considering their potential interaction. Moreover, the mediating role of RC in the BMI-hypertension relationship remains largely unexplored. Given the rising prevalence of obesity and dyslipidemia and addressing this gap, understanding the interaction between RC, BMI, and hypertension is essential for developing targeted prevention strategies, and our study aims to investigate the independent and joint associations of RC and BMI with hypertension risk, as well as the potential mediating role of RC in the BMI-hypertension relationship. We hypothesize that elevated RC and BMI are both associated with an increased risk of hypertension, and their combined effect may further amplify this risk. By elucidating these associations, our findings may provide valuable insights into potential therapeutic targets for hypertension prevention and management.

Materials and Methods

Study Design and Participants

This study is a secondary analysis of the China Health and Retirement Longitudinal Study (CHARLS), a national, population-based cohort targeting Chinese adults aged 45 and above (http://charls.pku.edu.cn/). The sample was drawn from 150 counties or districts and 450 villages across 28 provinces in China, spanning the period from 2011 to 2020.[16]

Throughout the CHARLS 2011–2020 cycle, the study encompassed 96, 137 participants, following the application of exclusion criteria. Participants aged 45 or older with complete data on blood lipids, and body mass index (BMI) were included in the analysis. Individuals with a prior history of hypertension at baseline were excluded. Exclusion criteria involved missed sex, hemoglobin, education, residence, glucose, blood lipids, smoke status, alcohol drink, diabetes mellitus, heart disease status, dyslipidemia related data (Figure 1).

Assessment of BMI and Remnant Cholesterol

Participants were instructed to fast overnight prior to blood sample collection. The collected blood samples were initially stored at local hospitals before being transported to Peking University in Beijing, where they were preserved at −80°C for subsequent analysis. Triglycerides, total cholesterol, LDL-C, HDL-C, and glucose levels were determined using an enzymatic colorimetric method on the Olympus Automatic Biochemical Analyzer (Hitachi 747).[17] The coefficients of variation were less than 4.0% for triglycerides and HDL-C, under 3.0% for total cholesterol, and below 5.0% for fasting glucose. Non-HDL-C was calculated by subtracting HDL-C from total cholesterol, while remnant cholesterol was defined as non-HDL-C minus LDL-C.[18] Body mass index (BMI) was derived from participants' height and weight measurements by dividing weight in kilograms by the square of height in meters. BMI was classified into two groups: non-obesity (BMI < 28.0 kg/m^2) and obesity (BMI ≥ 28.0 kg/m^2).[19]

Assessment of New-Onset Hypertension and Their Follow-up Time

Hypertension was defined as new-onset hypertension that developed during the follow-up period. It was mainly characterized by a medical diagnosis of hypertension based on self-reported questionnaires, or reported the use of antihypertensive medications, or blood pressure over 140/90 mmHg.[20] The time of hypertension onset was considered the time of the first diagnosis.

The occurrence of hypertension was calculated in different cases. For participants who did not report hypertension at their most recent follow-up, the event timing was determined as the difference between the year of the last survey and the baseline year. For those who did develop hypertension, the timing was based on the difference between the earliest reported year of hypertension onset and the baseline year.[21]

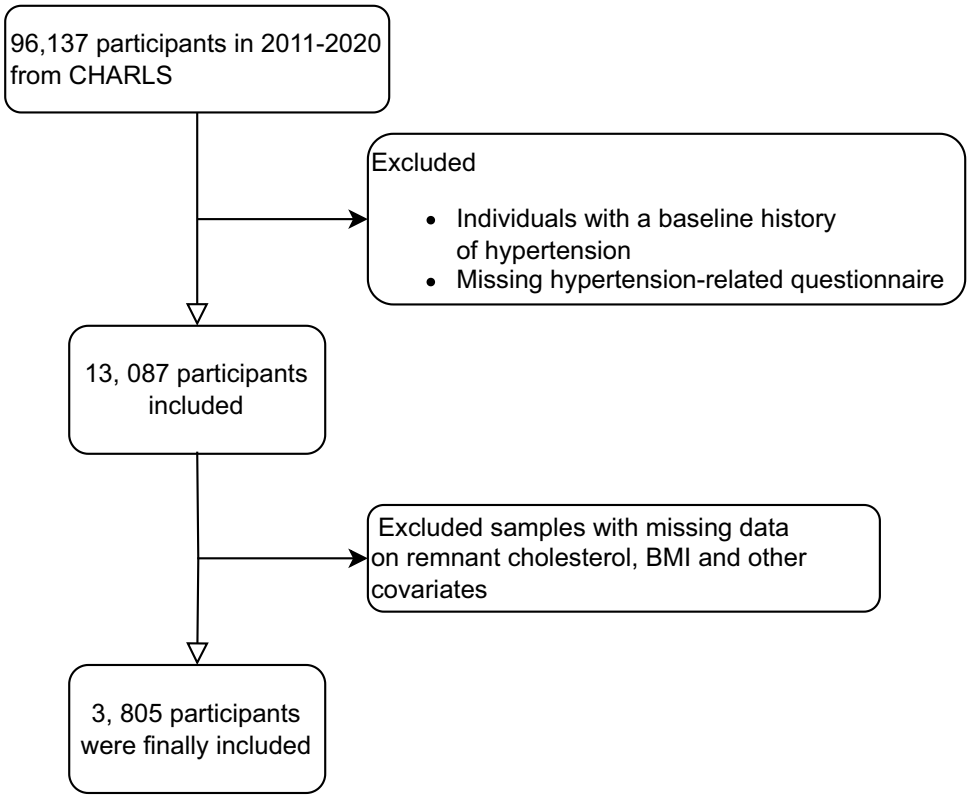

Figure 1 Flowchart of participant screening.

Covariate

According to prior research and clinical experts, potentially confounding and modifying variables were identified as follow: age, sex (male or female), residence (urban, rural), education (less than high school, high school, college). Clinical indicators such as eGFR, hemoglobin and glucose were measured in the laboratory. Heart disease and dyslipidemia were evaluated through a standardized questionnaire that inquired whether participants had ever been diagnosed by a doctor with these conditions.[22] Alcohol drinking status was classified into two distinct categories as ever/present or never. Smoke status was defined as former smoke but now quit, still smoke and never smoke.[23,24]

Statistical Analysis

Data were presented as means and standard deviations (SDs) for continuous variables with normal distributions and as medians with interquartile ranges for those that were non-normally distributed. Categorical variables were described as frequencies with percentages. Baseline characteristics between groups were compared using the chi-squared test, analysis of variance (ANOVA), or the Kruskal–Wallis rank-sum test, depending on the type of data.[25]

We calculated the follow-up person-time for each participant, starting from the baseline survey (2011–2012) until either the date of hypertension diagnosis or the end of follow-up (2019–2020), whichever occurred first. The incidence rates of hypertension events were expressed as the number of cases per 1000 person-years.[26] Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes associated with BMI (<28.0 kg/m^2 and ≥28.0 kg/m^2) and remnant cholesterol (RC, categorized into tertiles). Three models were developed: Model 1 adjusted for age, sex, BMI, education, smoking, and alcohol consumption; Model 2 included the adjustments from Model 1 plus diabetes history, eGFR, LDL, glucose, heart disease, dyslipidemia, hemoglobin and residence. We also used 3-knot restricted cubic spline (RCS) regression to explore potential nonlinear associations.

To evaluate the combined associations, participants were stratified into six groups based on their BMI (<28.0 kg/m^2 and ≥28.0 kg/m^2) and RC levels (categorized into 3 groups). In these groups, hazard ratios (HRs) for hypertension incidence were

calculated, using individuals with a BMI of <28.0 kg/m^2 and RC in sextile 1 as the reference group. We used the Kaplan-Meier survival curve to estimate the median hypertension-free survival time of the population (Figure 2A–C) and conducted a multivariable Cox regression analysis to examine associated risk factors (Table 1). We applied the least absolute shrinkage and selection operator (LASSO) regression model. In LASSO model, we used the method of cross-validation for model evaluation in Model 3 of cox regression analysis.

A mediation analysis and interactive analysis was conducted to evaluate the direct and indirect effects between BMI and hypertension through elevated RC. The mediating role of RC on the relationship between BMI and hypertension was similarly analyzed. To address potential confounding, we calculated the E-value, defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain the observed association as sensitivity analyses. The use of DAG analysis combined with the bootstrap method for mediation was an appropriate approach to explore the relationship between BMI, RC, and hypertension after adjustment for covariates. All statistical analyses were performed using R software (version 4.2.1). Mediation analysis utilized the 'mediation' and 'charlsR' package, while Cox regression was carried out using the 'survival' package. A two-sided P-value of <0.05 was considered statistically significant.[27]

Results

Study Participants and Baseline Characteristics

The final cohort consisted of 3,805 adults, of whom 590 were identified as having hypertension (Table 2). The mean age was 56.97 ± 8.66 years, with males comprising 44.26% of the sample. In the hypertension group, there was a higher proportion of older individuals, those with elevated BMI, lower eGFR, lower levels of educational attainment, a higher prevalence of heart disease, more participants living in rural areas, and elevated levels of blood glucose and lipids, including remnant cholesterol.

Correlation Between RC, BMI and Hypertension

The relationships between these factors and hypertension were further examined using restricted cubic spline (RCS) curves, illustrated in Figure 3A and B. The RCS analysis demonstrated a significant association between BMI, treated as a continuous variable, and an increased adjusted risk of hypertension ($P_{overall} < 0.001$, $P_{non\text{-}linear} = 0.0038$) in Figure 3A. In contrast, the relationship between remnant cholesterol (RC) and hypertension was linear but also statistically significant ($P_{overall} = 0.0116$, $P_{non\text{-}linear} = 0.6875$) in Figure 3B, indicating that both elevated and reduced levels of RC may contribute to a higher risk of hypertension.

Associations of RC, BMI and Cumulative RC-BMI with Hypertension

Over a maximum follow-up period of 9.0 years, 590 participants (15.51%) developed hypertension. Figure 2 shows Kaplan–Meier curves illustrating the cumulative incidence of hypertension among all participants. Those with higher RC levels had a significantly elevated risk of hypertension (P = 0.0034) (Figure 2A). Similarly, participants with higher BMI

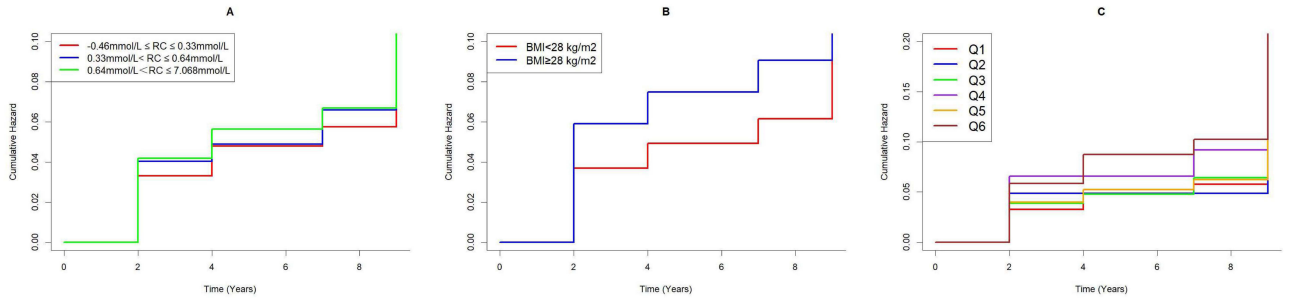

Figure 2 K–M plot of hypertension by RC and BMI subgroups. (**A**) Categorized by RC subgroups. (**B**) Categorized by BMI. (**C**) Categorized by joint variable of RC and BMI: Q1: BMI<28.0 kg/m^{2}and-0.46 mmol/L≤RC≤0.33 mmol/L; Q2: BMI≥28.0 kg/m^{2}and-0.46 mmol/L≤RC≤0.33 mmol/L; Q3: BMI<28.0 kg/m^{2}and0.33 mmol/L<RC≤0.64 mmol/L; Q4: BMI≥28.0 kg/m^{2}and0.33 mmol/L<RC≤0.64 mmol/L; Q5: BMI<28.0 kg/m^{2}and0.64 mmol/L<RC≤7.068 mmol/L; Q6: BMI≥28.0 kg/m^{2}and0.64 mmol/L<RC≤7.068 mmol/L.

Table 1 Baseline Characteristics of Participants

	Overall (n=3, 805)	***Non-Hypertension* (n=3, 215)**	***Hypertension* (n=590)**	***P* value**
Age (years)	56.97 ± 8.66	56.66 ± 8.59	58.68 ± 8.82	<0.0001
Sex (Male %)	1684(44.26)	1441(44.82)	243(41.19)	0.11
BMI (kg/m^2)	22.81 ± 3.49	22.68 ± 3.46	23.51 ± 3.55	<0.0001
Hemoglobin (g/dL)	14.22 ± 2.17	14.19 ± 2.15	14.41 ± 2.26	0.03
Education (%)				<0.01
Less Than High School	3424(89.99)	2873(89.36)	551(93.39)	
College	39 (1.02)	39 (1.21)	-	
High School	342 (8.99)	303 (9.42)	39 (6.61)	
Residence				0.01
Rural	2633(69.20)	2198(68.37)	435(73.73)	
Urban	1172(30.80)	1017(31.63)	155(26.27)	
Glucose (mg/dL)	105.53 ± 27.28	104.79 ± 25.53	109.55 ± 35.06	<0.01
Creatinine (mg/dL)	0.76 ± 0.17	0.76 ± 0.17	0.76 ± 0.18	0.73
eGFR (mL/min/1.73m^2)	98.39 ± 12.81	98.67 ± 12.75	96.87 ± 13.01	<0.01
Uric acid (mg/dL)	4.25 ± 1.15	4.24 ± 1.15	4.30 ± 1.18	0.27
Dyslipidemia (%)	174 (4.57)	142 (4.42)	32 (5.42)	0.33
HDL-C (mmol/L)	1.36 ± 0.39	1.37 ± 0.39	1.35 ± 0.40	0.53
LDL-C (mmol/L)	2.98 ± 0.86	2.96 ± 0.86	3.06 ± 0.87	0.01
RC (mmol/L)	0.60 ± 0.57	0.59 ± 0.56	0.67 ± 0.63	<0.01
Smoke status (%)				0.56
Former, now quit	270 (7.10)	227 (7.06)	43 (7.29)	
Never	2387(62.73)	2007(62.43)	380(64.41)	
Current	1148(30.17)	981(30.51)	167(28.31)	
Alcohol drink (%)				0.62
No	2533(66.57)	2146(66.75)	387(65.59)	
Yes	1272(33.43)	1069(33.25)	203(34.41)	
Diabetes Mellitus (%)	98 (2.58)	77 (2.40)	21 (3.56)	0.13
Heart disease = yes (%)	234 (6.15)	182 (5.66)	52 (8.81)	<0.01
Follow up time (years)	8.64 ± 1.46	9.00 ± 0.00	6.70 ± 3.04	<0.0001

Abbreviations: BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; RC, remnant cholesterol.

Table 2 Risk Classification of Hypertension Based on BMI and Remnant Cholesterol by Multiple Cox Regression Analysis

	Model 0	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
BMI	1.05(1.03,1.08) ***	1.07(1.05,1.09) ***	1.06(1.04,1.08) ***	1.06(1.04,1.08) ***
Non-obesity	Ref	Ref	Ref	Ref
Obesity	1.60 (1.22,2.10) ***	1.67(1.27,2.19) ***	1.60(1.21,2.12) ***	1.62(1.23,2.15) ***
Remnant Cholesterol	1.21(1.08,1.35) ***	1.22(1.09,1.37) ***	1.21(1.07,1.37) **	1.23(1.08,1.41) **
−0.46≤RC≤0.33	Ref	Ref	Ref	Ref
0.33<RC≤0.64	1.16(0.95,1.43)	1.16(0.94,1.42)	1.13(0.92,1.39)	1.15(0.93,1.42)
0.64<RC≤7.068	1.41(1.15,1.72) ***	1.42(1.17,1.74) ***	1.37(1.11,1.68) **	1.41(1.13,1.76) **

(*Continued*)

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Table 2 (Continued).

	Model 0	Model 1[a]	Model 2[b]	Model 3[c]
Joint variable				
Q1	Ref	Ref	Ref	Ref
Q2	1.12(0.49,2.52)	1.24(0.55,2.80)	1.16 (0.51,2.62)	1.20 (0.53,2.71)
Q3	1.13(0.91,1.40)	1.12(0.91,1.39)	1.10 (0.89,1.37)	1.12(0.91,1.40)
Q4	1.79(1.09,2.95) *	1.92(1.16,3.17) *	1.81(1.09,3.01) *	1.94(1.16,3.25) *
Q5	1.34(1.08,1.65) **	1.36(1.10,1.67) **	1.31(1.05,1.62) *	1.36(1.08,1.72) *
Q6	2.08(1.44,2.99) ***	2.12(1.47,3.06) ***	2.05(1.41,2.98) ***	2.18(1.48,3.21) ***

[a]Model 1 adjusted for age, sex, education, smoke, alcohol drink. [b] Model 2 adjusted for age, sex, education, smoke, alcohol drink, diabetes mellitus, eGFR, LDL, glucose, heart disease, dyslipidemia, hemoglobin, residence. [c] Model 3 adjusted for hemoglobin, glucose, HDL, LDL, BMI, age, residence, smoke, drink, heart disease. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Q1: BMI<28.0 kg/m^2&-0.46 mmol/L≤RC≤0.33 mmol/L. Q2: BMI≥28.0 kg/m^2&-0.46 mmol/L≤RC≤0.33 mmol/L. Q3: BMI<28.0 kg/m^2&0.33 mmol/L<RC≤0.64 mmol/L. Q4: BMI≥28.0 kg/m^2&0.33 mmol/L<RC≤0.64 mmol/L. Q5: BMI<28.0 kg/m^2&0.64 mmol/L<RC≤7.068 mmol/L. Q6: BMI≥28.0 kg/m^2&0.64 mmol/L<RC≤7.068 mmol/L.

exhibited a significantly increased risk of hypertension (P = 0.00079) (Figure 2B). Additionally, the combined effect of RC and BMI was positively associated with hypertension risk (P = 0.00069) (Figure 2C).

A multivariable Cox regression analysis was then performed to assess the relationship between RC, BMI, and their combined effect on hypertension, as detailed in Table 1. A risk prediction model based on LASSO regression, was created to identify risk factors that possessed the closest relations with hypertension in Figure 4 as follows. The selected risk factors include RC, hemoglobin, glucose, HDL, LDL, BMI, age, residence, smoke, drink, heart disease, and we used above risk factors as covariates to make cox regression analyses in Table 1—Model 3. Both RC and BMI, treated as continuous variables, were found to be associated with an increased risk of hypertension. Initially, in the baseline model (Model 0), BMI was categorized into two groups: non-obesity (BMI <28.0 kg/m^2) and obesity (BMI ≥28.0 kg/m^2). Individuals in the obesity group had a significantly higher risk of developing hypertension compared to the non-obesity group (P <0.001). These associations remained significant after adjusting for age, sex, education, smoke, alcohol drink, diabetes mellitus, eGFR, LDL, glucose, heart disease, dyslipidemia, hemoglobin and residence.

Similarly, when RC was divided into three groups in the baseline model (Model 0), participants in the highest RC group (0.64 mmol/L < RC ≤ 7.068 mmol/L) exhibited a significantly higher risk of hypertension compared to those in the lowest RC group (P <0.001). These significant associations persisted after adjusting for covariates in subsequent models (Model 1 and 2).

A joint analysis was then conducted to investigate the combined effects of RC and BMI on hypertension. The results revealed that individuals with both high BMI and high RC had the greatest risk of hypertension (Table 1). Specifically, compared to those with non-obesity and the lowest RC tertile (−0.46 mmol/L ≤ RC ≤ 0.33 mmol/L), participants with obesity and the highest RC tertile (0.64 mmol/L < RC ≤ 7.068 mmol/L) had a hazards ratio (HR) of 2.18 (1.48,3.21) for hypertension risk, even after adjusting for covariates.

Mediation Analyses of BMI and RC with Hypertension

Figure 5 illustrated the mutual mediation effects between BMI, RC, and hypertension. RC significantly mediated 7.07% of the association between high BMI and hypertension, while BMI simultaneously mediated 29.3% of the association between RC and hypertension.

Sensitivity Analyses

For the BMI analysis, the obesity group had an E-value of 2.58, while the T3 group of remnant cholesterol (0.64<RC≤7.068) had an E-value of 2.08. For the joint effect of BMI and RC, the Q6 group (BMI≥28.0 kg/m2 and 0.64 mmol/L<RC≤7.068 mmol/L) had an E-value of 3.52.

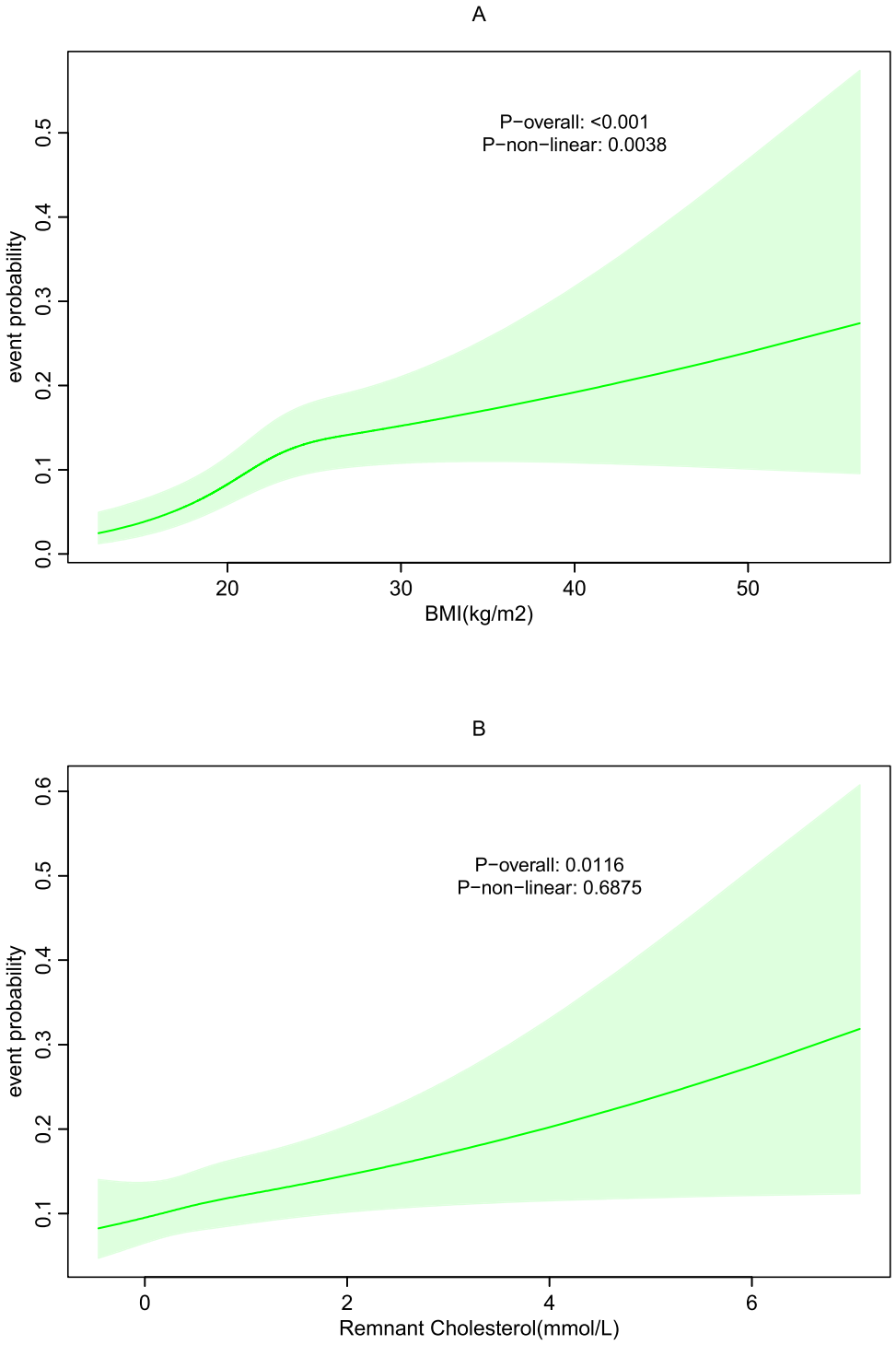

Figure 3 (**A**) Restricted cubic spline (RCS) for the association between BMI with the risks of hypertension. (**B**) RCS for the association between remnant cholesterol (RC) with the risks of hypertension.

Interaction Analysis of BMI and RC on New-Onset Hypertension

No significant multiplicative or additive interactions were observed between BMI and RC in relation to new-onset hypertension in Table 3 (Additive: RERI = −0.13, 95% CI −0.85 to 0.39; AP = −0.07, 95% CI −0.45 to 0.20; SI = 0.87, 95% CI 0.47 to 1.60).

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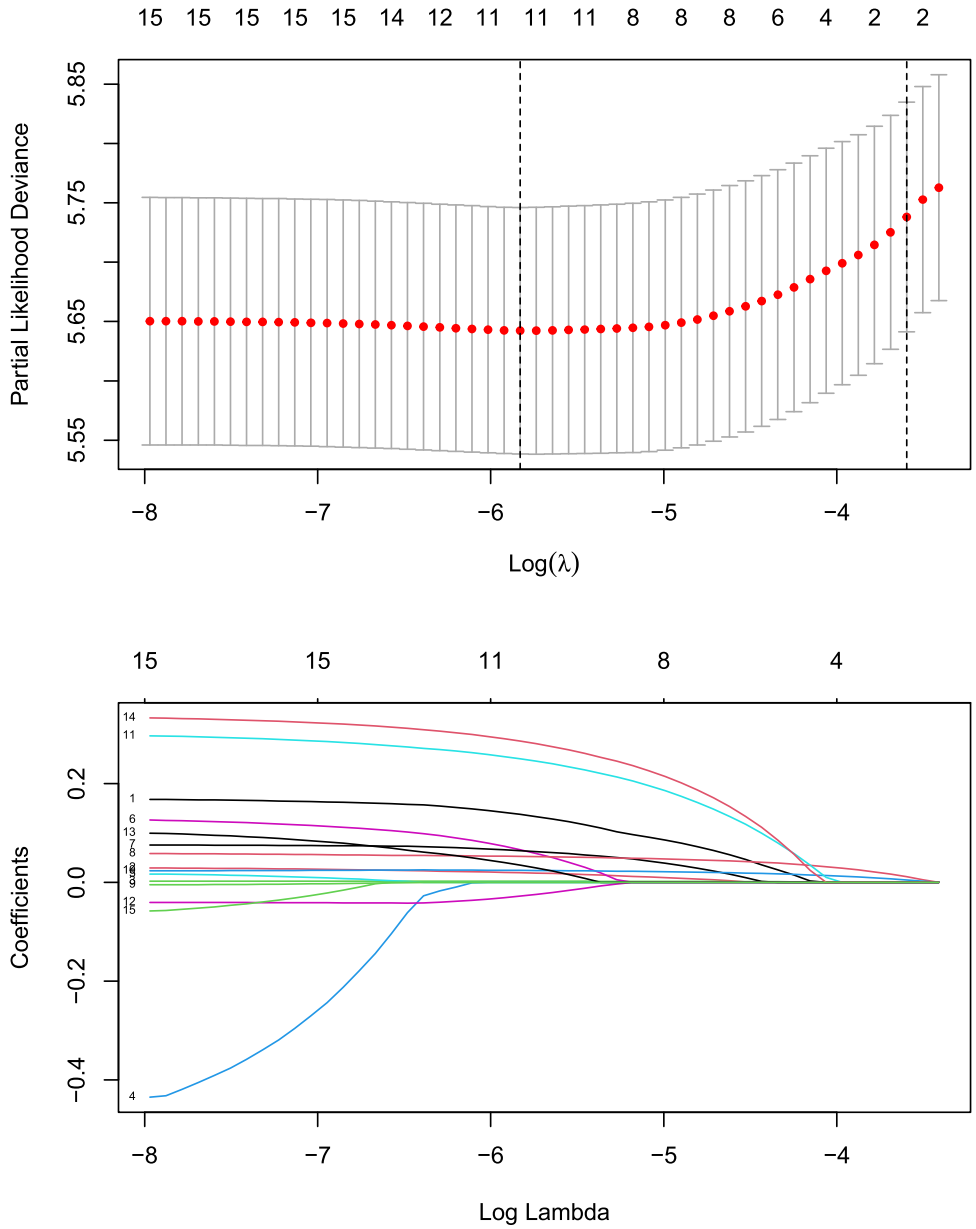

Figure 4 Risk factors possessed the closest relations with hypertension by LASSO regression.

Discussion

Hypertension is a major global health burden, contributing to cardiovascular diseases, stroke, and chronic kidney disease, particularly in aging populations with comorbid conditions like diabetes and dyslipidemia.[28,29] Recent studies show a high prevalence of untreated hypertension, which exacerbates the risk of cardiovascular complications.[30] Li et al found that hypertension combined with metabolic disorders significantly increases the risk of ischemic stroke.[31] Our study aligns with these findings, demonstrating that both RC and BMI jointly contribute to hypertension risk. Addressing these factors through lifestyle modifications and targeted interventions is crucial to reduce the burden of hypertension-related diseases.

Emerging evidence underscores the critical role of dyslipidemia, particularly RC, in the development of hypertension. RC, a component of atherogenic lipoproteins, has been shown to be closely associated with cardiovascular risk, independent of traditional lipid markers such as LDL-C and HDL-C.[32,33] Several large-scale epidemiological studies have confirmed the association between elevated RC levels and an increased risk of hypertension. In a study by Wu et al, RC was shown to be superior to other lipid-related parameters in predicting the risk of cardiometabolic disease in

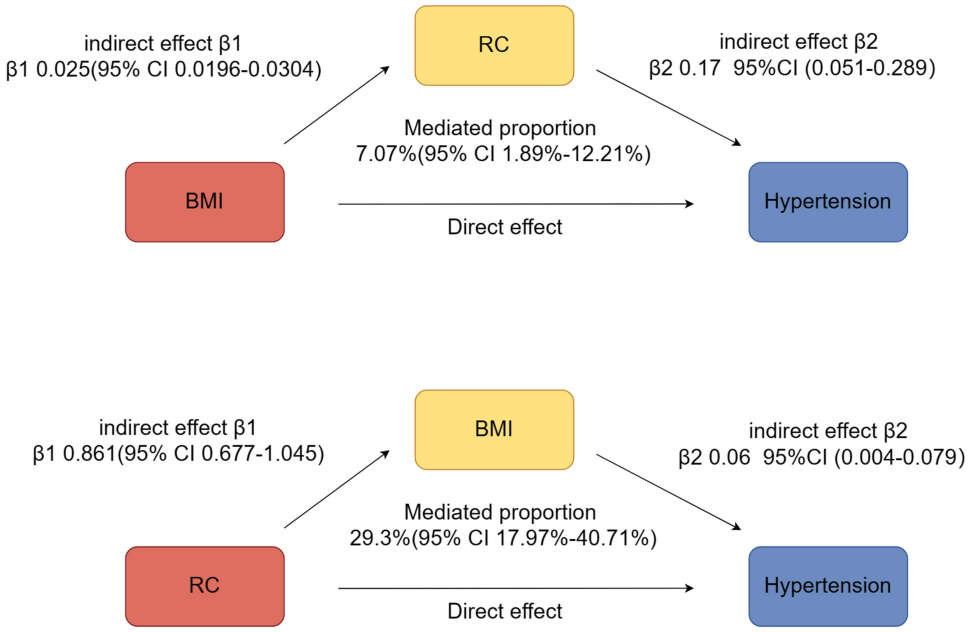

Figure 5 Mediation analyses of BMI and RC with hypertension.

individuals with hypertension.[34] Similarly, Shi et al demonstrated that RC was independently associated with hypertension, beyond the effects of LDL-C, in the general US adult population.[8] Mechanistically, RC may contribute to hypertension through multiple pathways. One major pathway is endothelial dysfunction, where RC interferes with nitric oxide availability, leading to impaired vasodilation.[32] Furthermore, RC is known to promote oxidative stress and inflammation within the vascular endothelium, which can result in increased arterial stiffness. This stiffening of arteries elevates systemic vascular resistance, contributing to the pathophysiology of hypertension.[35,36] Additionally, the accumulation of RC in arterial walls accelerates the progression of atherosclerosis, which further compromises vascular function, creating a vicious cycle that sustains elevated blood pressure.[37]

BMI is another key factor that has been strongly correlated with hypertension. Extensive research has established a dose-dependent relationship between higher BMI and the risk of hypertension. RCTs have consistently demonstrated that overweight and obese individuals who undergo weight loss interventions, whether through bariatric surgery or anti-obesity medications such as liraglutide, are more likely to achieve better control of hypertension.[38,39] The mechanisms linking BMI to hypertension are multifaceted and involve both direct and indirect pathways. One of the primary mechanisms is the activation of the sympathetic nervous system, which is more pronounced in individuals with higher BMI. This heightened sympathetic activity leads to increased renal sodium reabsorption and renin release, both of which contribute to higher blood pressure.[40] Additionally, adipose tissue, particularly visceral fat, acts as an endocrine organ, releasing pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which promote systemic inflammation.[41,42] This inflammatory state further exacerbates endothelial dysfunction and impairs vascular tone regulation, directly contributing to the development of hypertension. Obesity is also closely linked to

Table 3 Interaction Analysis of BMI and RC on New-Onset Hypertension

	HR [95% CI]	**HR [95% CI]**
Multiplicative scale	0.86 [0.61, 1.22]	1.05 [0.76, 1.45]
RERI	−0.13[−0.85, 0.39]	
AP	−0.07 [−0.45, 0.20]	
SI	0.87 [0.47, 1.60]	

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insulin resistance, a condition that amplifies the effects of hypertension through mechanisms such as hyperinsulinemia, which promotes sodium retention and enhances sympathetic nervous activity.[43]

Although RC mediated 7.07% of the association between BMI and hypertension, this proportion, while relatively small, remains clinically relevant. The modest mediation effect suggests that additional pathways may be involved in linking obesity to hypertension. Insulin resistance and chronic low-grade inflammation, both of which are closely associated with obesity, have been implicated as potential contributors to elevated blood pressure.[44,45] Insulin resistance may promote hypertension through increased renal sodium retention and sympathetic nervous system activation, while inflammatory mediators such as IL-6 and TNF-α can impair vascular function and promote arterial stiffness.[41,42] Future studies integrating multiple mediators may help clarify the relative contributions of these mechanisms and provide a more comprehensive understanding of the metabolic pathways underlying hypertension.

The relationship between RC and BMI and their combined effect on hypertension is of growing interest, particularly given their overlapping metabolic pathways. Although studies examining the joint effects of BMI, RC, and hypertension are limited, our findings are generally consistent with previous research. Wang et al found an S-shaped association between BMI and hypertension in elderly patients with dyslipidemia, with the highest risk observed in individuals with BMI between 24 and 29 kg/m^2.[46] Tang et al further reported a significant interaction between overweight/obesity and dyslipidemia, showing that individuals with both conditions had a much higher risk of hypertension than those with either factor alone.[47] Mohseni et al expanded on this by highlighting the synergistic effect of central obesity and dyslipidemia on hypertension, emphasizing that their co-existence amplifies the risk beyond their independent contributions.[2] Mediation analyses suggest that RC may partly mediate the relationship between high BMI and hypertension. Specifically, obesity-induced dyslipidemia, characterized by elevated RC levels, may promote the development of hypertension through mechanisms similar to those described above—namely, endothelial dysfunction, increased arterial stiffness, and systemic inflammation. High BMI can exacerbate the effects of elevated RC by promoting insulin resistance and metabolic syndrome, both of which are conditions that further disrupt lipid metabolism and enhance the hypertensive effects of RC.[48] Conversely, BMI may also mediate the relationship between RC and hypertension. Elevated RC levels have been shown to impair insulin sensitivity, and individuals with higher RC levels are more likely to develop obesity-related metabolic disturbances.[49] This reciprocal relationship suggests a bidirectional interaction where both RC and BMI potentiate each other's effects, creating a synergistic impact on the risk of hypertension.

This interaction is supported by joint analysis studies, which show that individuals with both high BMI and elevated RC levels have the greatest risk of developing hypertension. Our findings suggest that interventions targeting both RC and BMI simultaneously may be more effective in reducing hypertension risk compared to interventions focused on a single factor. Future studies are needed to further elucidate the complex interplay between lipid metabolism, obesity, and hypertension, and to explore potential therapeutic strategies aimed at modifying both RC and BMI to prevent and manage hypertension more effectively.

Several limitations should be acknowledged. First, as this study is observational, causal relationships between BMI, RC, and hypertension cannot be definitively established. Although mediation analysis suggests a potential pathway, residual confounding remains a concern, as unmeasured variables such as dietary habits, physical activity, and genetic predisposition may influence the observed associations. Second, hypertension was identified based on self-reported physician diagnoses and medication use, which may introduce misclassification bias. Similarly, other key covariates, including smoking, alcohol consumption, and comorbid conditions, were also self-reported, potentially leading to recall bias. Third, while BMI is a widely used indicator of adiposity, it does not fully capture fat distribution or muscle mass. Alternative metrics such as waist circumference or body fat percentage may provide a more nuanced assessment of obesity-related cardiovascular risk. Finally, our findings are based on a middle-aged and older Chinese population, and their generalizability to other ethnic groups or younger populations warrants further investigation. Future studies incorporating more comprehensive lifestyle data and objective measures of hypertension are needed to validate and extend our findings.

Conclusion

This study highlights the significant and interrelated roles of RC and BMI in the development of hypertension. Elevated RC, particularly in individuals with obesity, exacerbates hypertension risk, underscoring the need for a dual-focus

approach in hypertension prevention and management. Clinicians should consider incorporating RC assessments alongside BMI in routine cardiovascular risk evaluations. Lifestyle interventions, including dietary modifications, weight management, and physical activity, may be effective in reducing both RC and BMI, thereby lowering hypertension risk. Additionally, lipid-lowering therapies targeting RC, such as statins or emerging triglyceride-lowering agents, may be beneficial in high-risk populations.

Future research should focus on longitudinal studies with objective measures of blood pressure and adiposity to validate these findings and clarify causal relationships. Intervention trials evaluating the combined effects of RC-lowering strategies and weight management on hypertension risk are also warranted. Such studies will provide more robust evidence to inform targeted, evidence-based prevention and treatment strategies for hypertension.

Data Sharing Statement

The datasets used and/or analyzed in this research are publicly accessible or can be obtained from the corresponding author upon reasonable request at http://charls.pku.edu.cn/en.

Ethics Approval and Consent to Participate

The CHARLS study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of Peking University (IRB00001052-11015). The research involving human participants was approved by the Ethics Committee of Peking University. We also received approval from the Institutional Review Board of Zhuji Affiliated Hospital of Wenzhou Medical University (2024 [1021]). Written informed consent was obtained from all patients/participants prior to their involvement in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declared no conflicts of interest.

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