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Impact of remnant cholesterol to high-density lipoprotein cholesterol ratio on risk of incident ASCVD: the Kailuan prospective cohort study

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Abstract

Background The study utilized the remnant cholesterol (RC) to high-density lipoprotein cholesterol (HDL-C) ratio as a lipidemia indicator. Assessing its long-term impact on cardiovascular disease (ASCVD) is crucial for primary prevention.

Methods 84,380 participants were enrolled in the prospective cohort. Participants were classified into low, medium, and high levels based on baseline RC/HDL-C levels at the 50th percentile and 90th percentile. Participants were followed until December 31, 2023. Calculate the incidence density of ASCVD for each group. The time-dependent Cox proportional hazards model was utilized to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for ASCVD risk among different groups.

Results The study included 42,181, 33,739, and 8460 participants in the low, medium, and high levels respectively. A median follow-up of 16.92 years, 8397 ASCVD cases were identified. The 1000 person-years incidence density and 95% CIs for ASCVD were 5.86 (5.67, 6.05) in the low level, 6.92 (6.70, 7.15) in the medium level, and 8.85 (8.35, 9.39) in the high level. Compared to the low level, the Cox model showed that the HRs and 95% CIs for ASCVD were 1.09 (1.04, 1.14) and 1.23 (1.15, 1.32), respectively in medium and high levels.

Conclusion Higher RC/HDL-C level was significantly associated with an increased risk of ASCVD. Including the RC/HDL-C in lipid evaluation can reduce the onset of ASCVD.

Clinical trial registration number ChiCTR2000029767.

Keywords Dyslipidemia, ASCVD, Cohort

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Introduction

Cardiovascular disease (CVD) was the leading cause of death among Chinese in 2021 [1]. According to the report in 2020, the age-standardized mortality rate of CVD in China was 245.39/100,000 [2]. Atherosclerotic cardiovascular disease (ASCVD), the most common form of CVD, was reported to be on the rise in China in 2021 [3]. In addition, the 2020 report indicated that there is potential for further reduction in the age-standardized mortality rate of ischemic stroke. Which has only decreased by 3.3% compared to 1990 [4, 5]. Therefore, Implementing early preventive measures for ASCVD is crucial for reducing its overall disease burden.

Dyslipidemia is a modifiable risk factor for ASCVD [6, 7]. Current therapeutic approaches primarily involve the use of statins to manage low-density lipoprotein cholesterol (LDL-C) [8]. However, there remains a substantial proportion of dyslipidemia-related ASCVD cannot be adequately addressed [9, 10]. Remnant cholesterol (RC) is an untraditional lipidemia marker, comprising cholesterol from very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and chylomicrons [11]. It reflects the level of triglyceride-rich lipoproteins in plasma. Conversely, reduced high-density lipoprotein cholesterol (HDL-C) weakens the reverse cholesterol transport function [12]. In 1998, Masuoka et al. first proposed that the use of RC/ HDL-C could predict the occurrence of coronary heart disease (CHD) [13].

The RC/HDL-C is a lipid metabolism marker that reflects the imbalance between atherogenic and anti-atherogenic lipoproteins, indicating an imbalance favoring atherogenesis [14]. It has been applied in multiple large-scale population-based cohorts, including the National Health and Nutrition Examination Survey (NHANES) [15], the non-alcoholic fatty liver disease in Gifu Area, Longitudinal Analysis (NAGALA) cohort [16], and the Rich Healthcare Group Diabetes Cohort [17].

Several studies had demonstrated a positive association between the RC/HDL-C and conditions such as non-alcoholic fatty liver disease (NAFLD), Diabetes, and CHD [18–21]. While the association between RC/HDL-C and CHD has been previously reported, the evidence is mainly derived from small-sample cross-sectional study. This study examined the association between RC/HDL-C and the occurrence of new ASCVD, through a prospective cohort study.

Method

The participants were from the Kailuan cohort. Briefly, The Kailuan Cohort is located in Tangshan, Hebei Province, China, and it is carried out by the Kailuan community. The cohort commenced with the 2006 annual physical examination and continued follow-up until December 31, 2023 [22]. After that, the participants underwent a health examination every two years, and the outcome events were collected once every year. The most recent health examination took place in 2020 annual, and the outcome events were collected until December 31, 2023.

Participants' inclusion criteria were: (1) age ≥ 18 years; (2) population had completion of the 2006 annual health examination. There were exclusion criteria: (1) population had missing data on total cholesterol (TC), HDL-C, or LDL-C from the 2006 annual health examination; (2) population had a history of using lipid-lowering medication before the 2006 annual health examination; (3) population had a prior history of ASCVD before the 2006 annual health examination; (4) population weren't follow-up after the 2006 annual health examination and no recorded outcome event in the medical insurance database. The final cohort included 84,380 participants (Fig. 1).

Non-laboratory data included information from questionnaires and physical examinations. Questionnaire data were collected through interviews conducted by medical professionals and completed based on participants' self-reports. The questionnaire covered demographic information (age, gender, education level), behavioral habits (drinking, smoking, physical exercise), medical history (antihypertensive, antidiabetic, and lipid-lowering medications), as well as past illnesses and family history. Antihypertensive medications included diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). Antidiabetic medications included sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, non-insulin secretagogues, insulin preparations, traditional Chinese medicine, and others. Lipid-lowering medications included statins, fibrates, traditional Chinese medicine preparations, and other agents. Physical examination data, such as height, weight, and blood pressure, were measured by medical professionals. For further details, refer to previous research [22].

On the morning of the physical examination, participants provided a fasting venous blood sample of 5 mL. The samples were submitted for analysis four hours after collection. TC, HDL-C, LDL-C, triglycerides, fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), and serum creatinine levels were measured using an auto-analyzer (Hitachi 7600, Hitachi, Tokyo, Japan) [23]. The Estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [8]. RC was calculated as follows: RC = TC − HDL-C − LDL-C [24]. For further details, refer to previous research [22].

The cohort started with the 2006 annual physical examination and was followed up until December 31, 2023—a

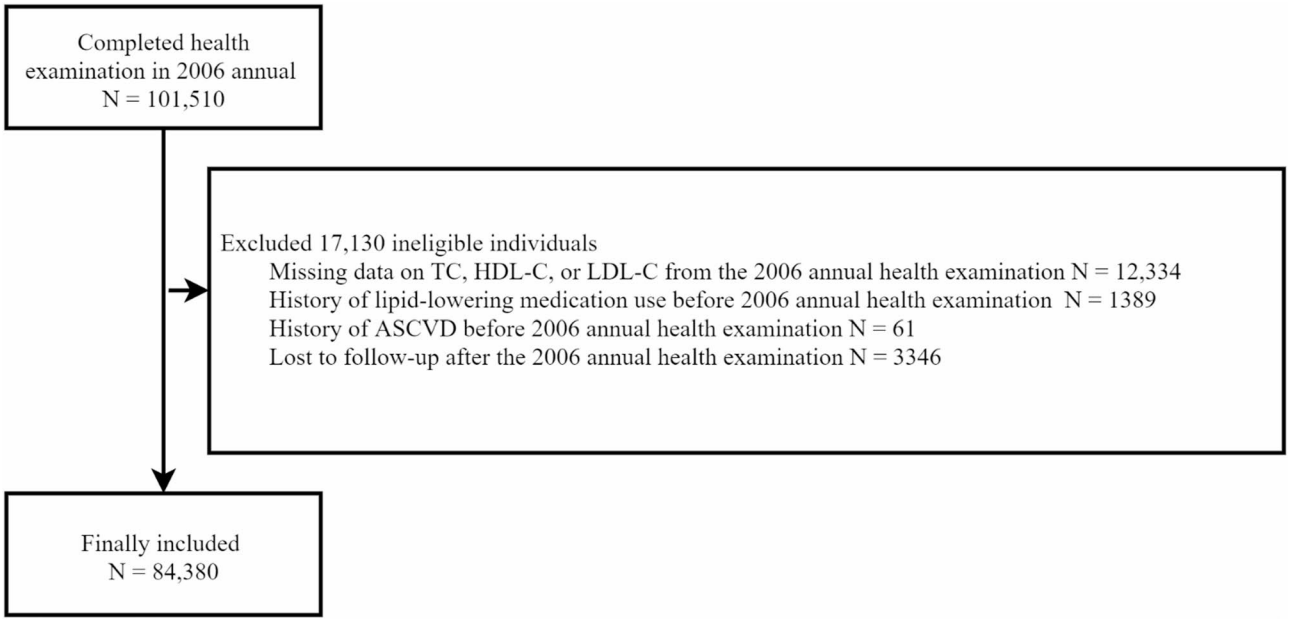

Fig. 1 Cohort participants' inclusion and exclusion flowchart. Remnant cholesterol (RC), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), atherosclerotic cardiovascular disease (ASCVD). This figure shows the inclusion and exclusion process for participants in the 2006 baseline cohort, resulting in 84,380 eligible individuals

total of 8 health check-ups (including 2006). The primary outcome was ASCVD, defined according to the International Classification of Diseases (10th Edition) to include Cerebral Infarction (CI) (I63) and Myocardial Infarction (MI) (I21) [25]. The outcome events were all determined by medical professionals, and the cases were checked and collected annually by the staff of Kailuan Cardiovascular Laboratory from the data of 11 affiliated hospitals of Kailuan Group and Tangshan Medical Insurance Center.

Smoking was divided into two categories, "current" and "non-current". "Smoking" was defined as consuming more than one cigarette per day for a consecutive year. Drinking was divided into two categories, "current" and "non-current". "Drinking" was defined as an average intake of at least 100 mL of spirits (with an alcohol content of 50% or higher) per day over a consecutive year. Educational level was divided into three categories, "below high school", "high school", and "college or above". Physical exercise was divided into three categories: "regular", "occasional", and "never". "Regular" was defined as exercise consisting of sessions lasting at least 30 minutes each, occurring three or more times per week. "Occasional" was defined as exercise do not meet the criteria for "regular", and "never" indicates that participants did not engage in exercise at all. Hypertension was defined as participants self-reported Hypertension, a history of antihypertensive medication use, or 2006 annual physical examination revealing a systolic blood pressure (SBP) greater than 140 mmHg or diastolic blood pressure (DBP) greater than 90 mmHg [26]. Diabetes was defined as participants' self-reported Diabetes, having a history of antidiabetic medication use, or the 2006 annual physical examination revealing a fasting blood glucose (FBG) greater than 7.0 mmol/L [27]. Lastly, "family history of CVD" was defined as a history of CVD in either parent, including Cerebral Hemorrhage (I61), CI (I63), or MI (I21).

Statistical analysis

Using R 4.0.4 and SAS 9.4 completed analysis. A Statistical significance level set at $P<0.05$ (two-sided). The pairwise comparisons were conducted using the Bonferroni-adjusted significance level, with a corrected α of 0.016.

Assuming the missing covariate data were random. The fully conditional specification imputation method was used for the missing. Using discriminant analysis for categorical variables, and regression modeling for continuous variables. The entire imputation process was performed in 20 iterations and 1 independent imputation dataset was generated. There were 7564 participants (0.09%) missing baseline covariate data. For the time-dependent variables (RC/HDL-C, TG, hs-CRP, eGFR) across eight health examinations, missing values were imputed using the previous year's non-missing values.

The cut points for RC/HDL-C levels were first explored by visualizing the distribution using a histogram. Subsequently, restricted cubic spline model was employed to examine the dose–response relationship between RC/

HDL-C and ASCVD, which informed the selection of optimal cut points.

The normality of continuous variables was assessed using the Anderson–Darling test. The continuous variables with a normal distribution are presented as mean (standard deviation), with a skewed distribution are presented as median (Q1, Q3), but categorical variables are presented as frequency (percentage). Group differences were using the Analysis of Variance (ANOVA) for normally distributed variables, the Kruskal-Wallis test for skewed variables, and the χ^2 test for categorical variables.

The incidence density was calculated using the formula: incidence density = (number of new cases/total Person-Years) × 1000. Kaplan-Meier (KM) curves were plotted, and comparison among groups was performed using the Log-rank test. Under the assumption of proportional hazards, the time-dependent Cox proportional hazards model was used to assess the impact of RC/HDL-C levels on ASCVD, reporting hazard ratios (HR), and 95% confidence intervals (CI).

ASCVD and time were set as dependent variables, and RC/HDL-C levels as independent variables, with adjustments made for influence factors. Model establishment followed the principle of adjusting for non-laboratory indicators to include laboratory indicators. Multicollinearity among candidate variables was assessed using the variance inflation factor (VIF) prior to inclusion in the model. Model 1 adjusted for gender (male/female) and age. Model 2 further adjusted BMI, SBP, drinking (current/non-current), smoking (current/non-current), education level (below high school/high school/college or above), physical exercise (never/occasional/regularly), use of antihypertensive medications (yes/no), use of antidiabetic medications (yes/no), and family history of CVD (yes/no) based on Model1. The natural logarithm (ln) transformation was applied to certain variables in Model 3 due to their skewed distributions. Model 3 further adjusted ln(FBG), ln(hs-CRP), ln(TG), and ln(eGFR) based on Model 2.

Analyzing the time-dependent effect, ASCVD and time were set as dependent variables, with each unit of RC/HDL-C as an independent variable, and adjustments were made for influencing factors. Model establishment followed the same principle as Models 1–3 above.

Participants were stratified by gender (male or female), age (≥ 60 years or < 60 years), or BMI (≥ 25 kg/m^2 or < 25 kg/m^2), and conducted the analysis based on the above Model 3. And validating the multiplicative interaction between stratified factors and groups.

Sensitivity analyses were conducted based on Model 3. As followed: (1) using data before imputing missing baseline covariate data; (2) excluding the population using antihypertensive medications at baseline; (3) excluding the population using antidiabetic medications at baseline; (4) excluding participants with follow-up < 1 years. The main analysis included the populations excluded in the sensitivity analyses.

The predictive performance model was assessed using Harrell's C index. China-PAR model included ln(age), ln(SBP), ln(HDL-C), ln(TC), ln(WC), ln(BMI), smoking, Diabetes, and family history of CVD [28]. Model 1 further adjusted RC/HDL-C based on the China-PAR model. Model 2 further adjusted RC/HDL-C*ln(age) based on the China-PAR model. The Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were used to assess differences in predictive ability between Models 1 and 2 compared to the China-PAR model reference.

Time-dependent receiver operating characteristic (ROC) curve analysis was conducted to evaluate the predictive ability of the RC/HDL-C ratio for ASCVD events at 3, 5, 7, and 9 years. The area under the curve (AUC) at each time point was calculated to assess the discriminative performance over time.

Results

84,380 participants were enrolled, with a mean age of 51.90 ± 12.68 years, comprising 81,110 males (79.80%). The distribution histogram of RC/HDL-C demonstrated a right-skewed pattern. Meanwhile, restricted cubic spline analysis indicated a linear dose–response relationship between RC/HDL-C and the outcome (Supplementary Fig. 1). Participants were grouped according to their baseline RC/HDL-C ratio. Low level included participants whose RC/HDL-C was below the 50th percentile (RC/HDL-C < 0.70), medium level included participants whose RC/HDL-C was between the 50th percentile and 90th percentile(0.70 ≤ RC/HDL-C < 1.72), and high level included participants whose RC/HDL-C at or above the 50th percentile 1.72 ≤ RC/HDL-C).

The low level had 42,181 participants, the medium level had 33,739, and the high level had 8460 participants. Baseline characteristics (Table 1), such as gender, age, and education level, revealed statistically significant differences across the three groups ($P < 0.001$). 17,130 individuals were excluded, with baseline characteristics provided in Supplementary Table 1.

The cohort follow-up person-years were 1,276,682.99 years, median was 16.92 years. During the follow-up, 8397 new ASCVD were identified (2002 MI and 6649 CI, with 254 cases occurred in both). The incidence densities of ASCVD for the low, medium, and high levels were 5.86 (5.67, 6.05), 6.92 (6.70, 7.15), and 8.85 (8.35, 9.39), respectively, as detailed in Table 2. A Statistically significant difference was found in the KM curves among the groups ($P < 0.001$), shown in Fig. 2.

All covariates included in the adjusted model had VIF values < 5, indicating acceptable levels of collinearity. The

Table 1 Baseline characteristics of participants

Characteristics	Low level *N* = 42,181	Medium level *N* = 33,739	High level *N* = 8460	*P*[*]
Male, n (%)	33,630 (79.73)	26,477 (78.48)	6699 (79.18) [ab]	< 0.001
Age, years	50.90 ± 12.92	51.82 ± 12.14	53.38 ± 10.74	< 0.001
BMI, kg/m^2	24.72 ± 3.35	25.22 ± 3.33	25.55 ± 3.31	< 0.001
Education level, n (%)				< 0.001
Below High school	33,207 (78.73)	25,554 (78.70)	7401 (87.48)	
High school	5815 (13.79)	6827 (13.62)	753 (8.90)	
College or above	3159 (7.49)	2763 (8.19)	306 (3.62)	
Physical exercise, n (%)				< 0.001
Never	4151 (9.84)	2918 (8.65)	512 (6.05)	
Occasional	30,233 (71.67)	25,925 (76.84)	7010 (82.86)	
Regular	7797 (18.48)	4896 (14.51)	938 (11.09)	
Current Drinking, n (%)	18,193 (43.13)	14,080 (41.73)	2568 (30.35)	< 0.001
Current Smoking, n (%)	17,627 (41.79)	13,725 (40.68) [a]	2671 (31.57)	< 0.001
SBP, mm Hg	130.63 ± 19.89	130.24 ± 19.35 [a]	132.29 ± 19.03	< 0.001
FBG, mmol/L	5.10 (4.65, 5.62)	5.15 (4.71, 5.76)	5.12 (4.59, 5.83) [a]	< 0.001
TG, mmol/L	1.11 (0.80, 1.52)	1.46 (1.00, 2.22)	1.66 (1.08, 2.62)	< 0.001
hs-CRP, mmol/L	0.68 (0.25, 1.70)	0.80 (0.30, 2.10)	1.41 (0.44, 5.74)	< 0.001
eGFR, mL/min/1.73 m^2	78.48 (66.22, 93.27)	83.20 (70.60, 96.22)	87.23 (74.70, 99.29)	< 0.001
Hypertension, n (%)	18,189 (43.12)	14,225 (42.16) [a]	4060 (47.99)	< 0.001
Diabetes, n (%)	3209 (7.61)	3394 (10.06)	1030 (12.17)	< 0.001
Antihypertensive medications, n (%)	4058 (9.62)	4032 (11.95)	900 (10.64) [a]	< 0.001
Antidiabetic medications, n (%)	833 (1.97)	875 (2.59)	211 (2.49) [ab]	< 0.001
Family history of CVD, n (%)	2403 (5.70)	2195 (6.51)	538 (5.18) [a]	< 0.001

Remnant cholesterol (RC), body mass index (BMI), systolic blood pressure (SBP), fasting blood glucose (FBG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), high sensitivity C-reactive protein (hs-CRP), and estimated glomerular filtration rate (eGFR). The continuous variables with a normal distribution are displayed as mean (standard deviation), continuous variables with a skewed distribution are shown as median (Q1, Q3), and categorical variables are presented as frequency (percentage). Differences between groups were tested using the Analysis of Variance (ANOVA) for normally distributed variables, the Kruskal-Wallis test for skewed variables, and the χ^2 test for categorical variables. Pairwise comparisons were adjusted using the Bonferroni correction ($\alpha = 0.016$)

[*] Comparison of the three groups. [a] Not significantly different from the low level. [b] Not significantly different from the medium level

Cox model 3 indicated, compared to the low level, the HRs (95%CIs) for ASCVD incident in the medium and high levels were 1.09 (1.04, 1.14) and 1.23 (1.15, 1.32), respectively. The HRs and 95%CIs for MI were 1.19 (1.08, 1.32) and 1.57 (1.37, 1.80). And for CI, the HRs (95%CIs) were 1.07 (1.01, 1.13) and 1.15 (1.06, 1.24). Each unit increase in RC/HDL-C was associated with HRs (95%CIs) for ASCVD of 1.12 (1.08, 1.15), for MI of 1.19 (1.11, 1.27), and for CI of 1.08 (1.04, 1.13), as detailed in Table 2.

Stratified by gender, no interaction was observed ($P = 0.376$). The Cox model, in the male, the HRs (95% CIs) for ASCVD in the medium and high level compared to the low level were 1.10 (1.05, 1.16) and 1.22 (1.13, 1.31), respectively; for the female, the HRs and 95% CIs were 1.01 (0.87, 1.16) and 1.28 (1.05, 1.56).

Stratified by age, no interaction was observed ($P = 0.131$). The Cox model, in the age ≥ 60 years, the HRs and 95% CIs for ASCVD in the medium and high levels compared to the low level were 1.17 (1.10, 1.24) and 1.38 (1.26, 1.50), respectively; for the age < 60 years, the HRs and 95% CIs were 1.04 (0.96, 1.12) and 1.20 (1.07, 1.35).

Stratified by BMI, no interaction was observed ($P = 0.612$). The Cox model, in the BMI < 25 kg/m^2, the HRs and 95% CIs for ASCVD in the medium and high levels compared to the low level were 1.10 (1.02, 1.18) and 1.24 (1.11, 1.38), respectively; for the BMI ≥ 25 kg/m^2, the HRs and 95% CIs were 1.09 (1.02, 1.16) and 1.22 (1.11, 1.34). Stratification analysis results were shown in Fig. 3 and Supplementary Table 2.

Four sensitivity analysis results stayed robust (Fig. 4, Supplementary Table 3). The China-PAR model had a Harrell's C index of 0.7217 (0.7168, 0.7266). In comparison, model 1 (adding RC/HDL-C) had an index of 0.7220 (0.7171, 0.7269), and model 2 (adding RC/HDL-C * ln(age)) was 0.7219 (0.7170, 0.7268), as shown in Table 3. The AUC of RC/HDL-C for predicting ASCVD was 0.762 at 3 years, 0.756 at 5 years, 0.749 at 7 years, and 0.746 at 9 years, indicating a consistently moderate predictive performance over time (Supplementary Fig. 2).

Discussion

The study investigated the association between RC/HDL-C levels and the onset of new ASCVD through a prospective cohort, taking into account long-term

Table 2 RC/HDL-C levels with the risk of ASCVD and subtype (HR and 95%CI)

	Low level	Medium level	High level	Per 1 Unit increase
ASCVD				
Case/Participants (n/N)	3755/42,181	3532/33,739	1110/8460	-
Incidence density (1,000 person-years)	5.86 (5.67, 6.05)	6.92 (6.70, 7.15)	8.85 (8.35, 9.39)	-
Non-adjusted Model	1.00	1.18 (1.13, 1.24)	1.51 (1.41, 1.62)	1.21 (1.18, 1.25)
Model 1	1.00	1.16 (1.10, 1.21)	1.41 (1.32, 1.51)	1.24 (1.20, 1.28)
Model 2	1.00	1.14 (1.10, 1.20)	1.38 (1.29, 1.47)	1.20 (1.16, 1.24)
Model 3	1.00	1.09 (1.04, 1.14)	1.23 (1.15, 1.32)	1.12 (1.08, 1.15)
Myocardial Infarction				
Case/Participants (n/N)	816/42,181	859/33,729	327/8460	-
Incidence density (1000 person-years)	1.24 (1.16, 1.33)	1.63 (1.53, 1.74)	2.51 (2.25, 2.80)	-
Non-adjusted Model	1.00	1.32 (1.20, 1.45)	2.02 (1.78, 2.30)	1.33 (1.26, 1.41)
Model 1	1.00	1.30 (1.18, 1.43)	1.90 (1.67, 2.16)	1.36 (1.28, 1.44)
Model 2	1.00	1.26 (1.15, 1.39)	1.83 (1.61, 2.09)	1.32 (1.24, 1.39)
Model 3	1.00	1.19 (1.08, 1.32)	1.57 (1.37, 1.80)	1.19 (1.11, 1.27)
Cerebral Infarction				
Case/Participants (n/N)	3034/42,181	2786/33,739	829/8460	-
Incidence density (1000 person-years)	4.70 (4.53, 4.87)	5.41 (5.21, 5.61)	6.51 (6.08, 6.96)	-
Non-adjusted Model	1.00	1.15 (1.09, 1.21)	1.38 (1.28, 1.49)	1.17 (1.13, 1.21)
Model 1	1.00	1.13 (1.07, 1.19)	1.29 (1.20, 1.39)	1.19 (1.15, 1.23)
Model 2	1.00	1.11 (1.06, 1.17)	1.27 (1.17, 1.37)	1.15 (1.11, 1.20)
Model 3	1.00	1.07 (1.01, 1.13)	1.15 (1.06, 1.24)	1.08 (1.04, 1.13)

Remnant cholesterol (RC), high density lipoprotein cholesterol (HDL-C), atherosclerotic cardiovascular disease (ASCVD), hazard ratio (HR), confidence interval (CI)

Model 1: Adjusted for age, and gender

Model 2: Expands on model 1 by further adjusting for BMI, SBP, drinking, smoking, educational level, physical exercise, CVD family history, use of antidiabetic medication, and use of antihypertensive medication

Model 3: Expands on model 2 by further adjusting for ln(FBG), ln(TG), ln(hs-CRP), and ln(eGFR)

changes. Finding RC/HDL-C levels significantly influenced the occurrence of ASCVD. Compared to the low level, the high level exhibited a 23% increase in ASCVD risk, a 57% increase in the risk of MI, and a 15% increase in the risk of CI. Additionally, it evaluated the predictive capacity of existing ASCVD models when incorporating RC/HDL-C.

Yang et al. conducted a cross-sectional study in China to investigate the association between lipid metabolism markers and intracranial atherosclerotic stenosis (ICAS), recruiting 658 ischemic stroke patients [19]. Their findings showed after adjusting for influencing factors, RC/HDL-C was a risk factor for ICAS, with an OR (95% CI) of 1.64 (1.01, 2.65), and the AUC (95% CI) for predicting ICAS was 0.544 (0.500, 0.589). Similarly, Wu et al. used a cross-sectional study to analyze the impact of RC/HDL-C on coronary CT-derived fractional flow reserve (FFRct) in 219 patients with coronary artery stenosis [29]. They found that the RC/HDL-C was a risk factor for FFRct ≤ 0.80, with an OR (95% CI) of 4.682 (1.197, 18.316). Both ICAS and coronary artery stenosis are risk factors for ASCVD, and the studies by Yang and Wu evaluated the association between RC/HDL-C and these ASCVD risk factors. This was consistent with the study that RC/HDL-C is associated with ASCVD risk, indicating that RC/HDL-C as a lipid metabolism marker, can assess ASCVD risk. However, its predictive capacity is relatively weak. Compared to case-control studies, this study provided stronger evidence regarding the causal relationship between RC/HDL-C and ASCVD.

No cohort study had yet directly explored the association between RC/HDL-C as a lipidemia marker and ASCVD risk. Sheng et al. conducted a 6.13-year follow-up study on 15,464 participants in China, evaluating the association between existing lipidemia markers and new-onset Diabetes [18]. Their results demonstrated that the unconventional lipidemia marker, RC/HDL-C, was the best indicator of Diabetes risk, with an HR (95% CI) of 6.75 (2.40, 18.98). They also used time-dependent ROC curves to assess the predictive ability of each marker, but RC/HDL-C's predictive power for Diabetes was not optimal, with a 12-year Diabetes prediction area under curves (AUC) of 0.652, compared to an AUC of 0.669 for the non-HDL/HDL-C ratio. Diabetes is an established risk factor for ASCVD, and having type 2 Diabetes for 10 years further increases the risk of ASCVD [10]. However, the relationship between RC/HDL-C, Diabetes, and

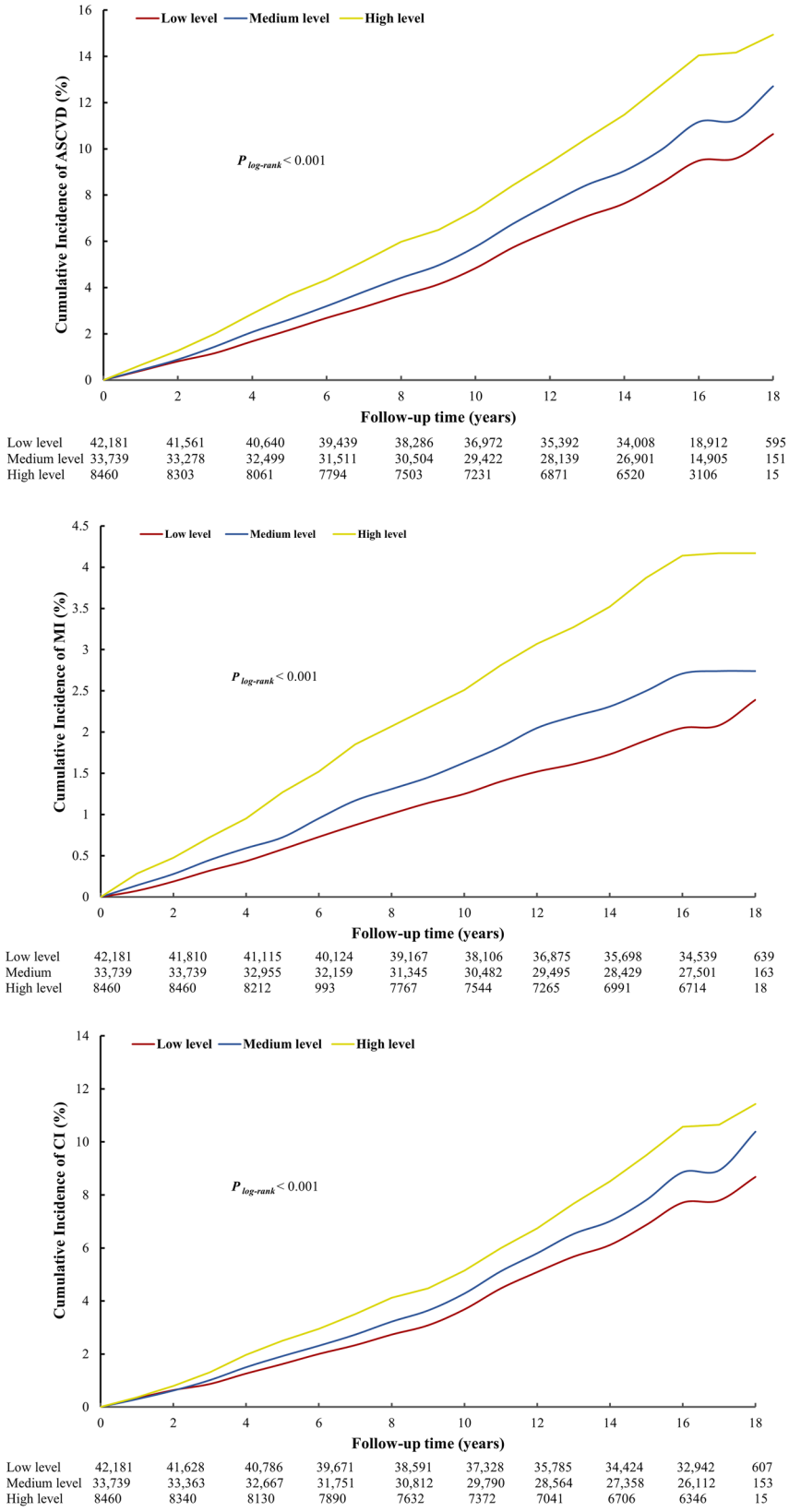

Fig. 2 Cumulative Incidence for different RC/HDL-C Levels. Remnant cholesterol (RC), high-density lipoprotein cholesterol (HDL-C), atherosclerotic cardiovascular disease (ASCVD), myocardial infarction (MI), cerebral infarction (CI). Higher RC/HDL-C levels were consistently associated with greater cumulative risk of ASCVD, MI, and CI over time

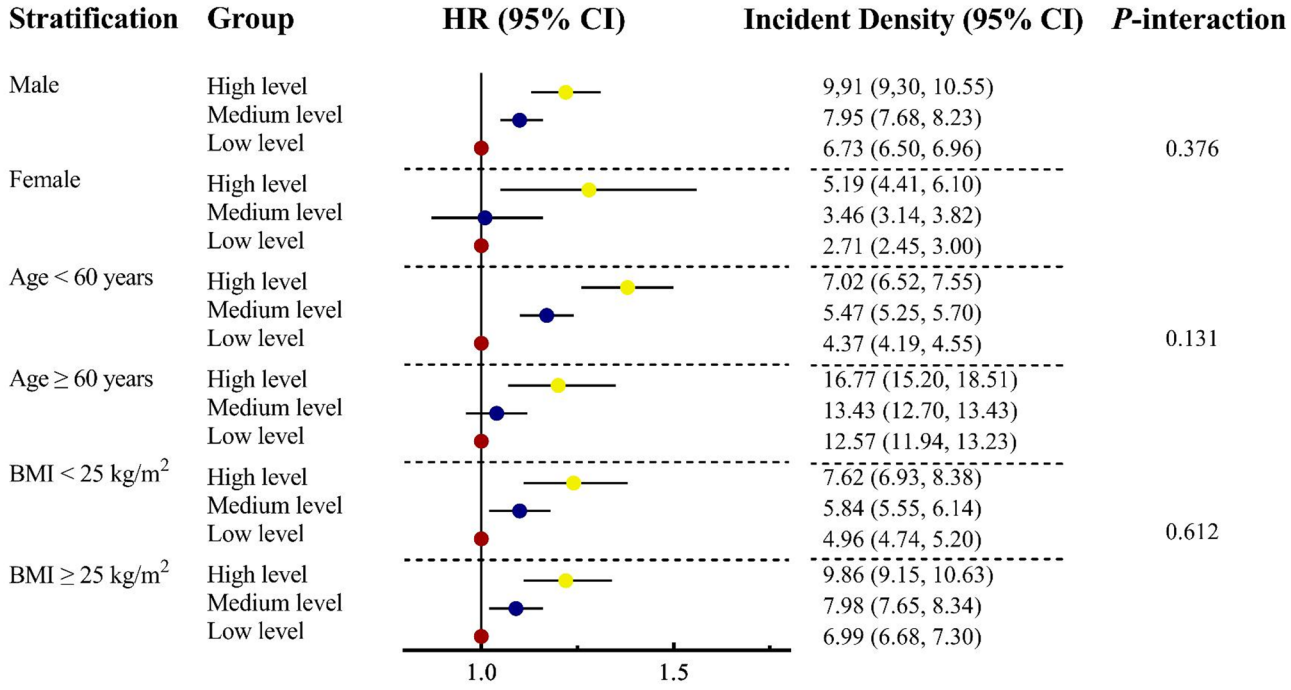

Fig. 3 Forest Plot for Stratification Analysis of RC/HDL-C Levels and ASCVD Risk. Remnant cholesterol (RC), high density lipoprotein cholesterol (HDL-C), atherosclerotic cardiovascular disease (ASCVD), hazard ratio (HR), confidence interval (CI), body mass index (BMI). Multivariate adjusted Model: Adjusted for age, gender, BMI, SBP, drinking, smoking, educational level, physical exercise, CVD family history, use of antidiabetic medication, and use of antihypertensive medication, ln(FBG), ln(TG), ln(hs-CRP), and ln(eGFR). Stratified by gender, all covariates except gender were included. Stratified by age, all covariates except age were included. Stratified by BMI, all covariates except BMI were included. *P*-interaction is the multiplicative interaction between stratified factors and the RC/HDL-C groups. This figure shows that higher RC/HDL-C levels are consistently associated with increased ASCVD risk across gender, age, and BMI subgroups

ASCVD still requires further investigation, particularly regarding the underlying disease mechanisms.

The stratified analysis revealed no multiplicative interaction between RC/HDL-C levels and gender, age, or BMI. First, gender stratification was performed due to differences in the gender composition of the cohort. After stratification, except for the medium level group in the female, the HRs for ASCVD were statistically significant in all groups. This may be partly attributable to the limitation of sample size. Additionally, the lack of predictive power observed in females may be explained by the protective effect of estrogen before menopause, which tends to elevate HDL-C levels [30]. As a result, a higher RC/HDL-C ratio might be required to indicate cardiovascular risk in premenopausal women. Second, in the age-stratified analysis, the HR for ASCVD in the medium-level group for the age < 60 years was not statistically significant, likely because the younger group was in generally better health, resulting in a lower ASCVD incidence. Or the grouping strategy may have masked the underlying trend, as the "medium level" category was artificially defined and could have included individuals who were actually at low or high risk. This misclassification may have diluted the observed effect. Lastly, in the BMI-stratified analysis, for the low level, the risk of ASCVD was consistently elevated in both overweight and non-overweight participants in the medium and high levels. After adjusting for the effects of gender, age, and BMI on ASCVD, the results indicated that the influence of RC/HDL-C levels was consistent across different populations.

Additionally, RC/HDL-C modestly improved the predictive ability for ASCVD, the practical significance of this enhancement was not substantial. Because the impact of lipidemia on the body was a result of long-term cumulative exposure, causing gradual damage to the vascular endothelium. Although RC/HDL-C's predictive power may be limited, it can still serve as a valuable indicator, contributing to a more comprehensive evaluation of lipidemia.

The underlying mechanisms influencing ASCVD onset can be examined from several perspectives. A higher RC/HDL-C ratio reflected either an increase in RC levels or a reduction in HDL-C levels, signaling an imbalance in lipid metabolism [31]. First, this imbalance signified that lipid deposition in the vascular wall exceeds the metabolic clearance rate, leading to plaque formation over time [32, 33]. Second, it increased oxidative stress in the body, resulting in endothelial dysfunction and accelerating the progression of atherosclerosis [34, 35]. Finally,

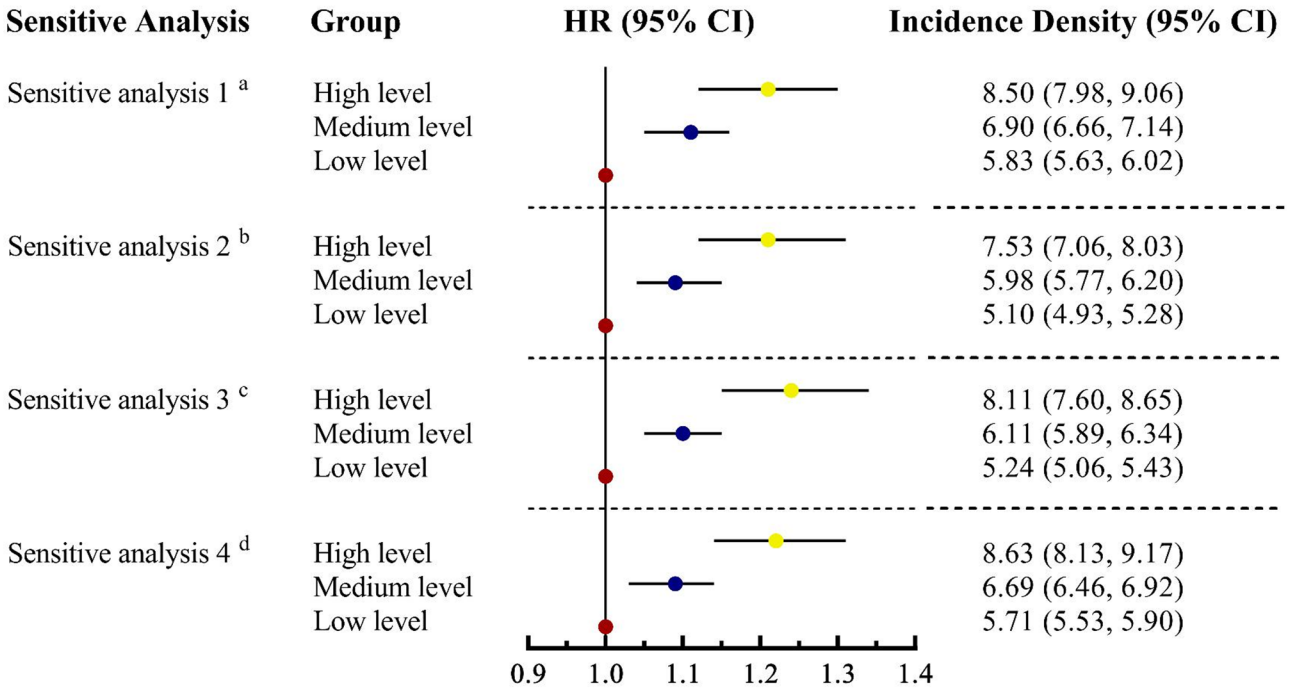

Fig. 4 Forest Plot for Sensitivity Analysis of RC/HDL-C Levels and ASCVD Risk. Remnant cholesterol (RC), high density lipoprotein cholesterol (HDL-C), atherosclerotic cardiovascular disease (ASCVD), hazard ratio (HR), confidence interval (CI). Multivariate adjusted Model: Adjusted for age, gender, BMI, SBP, drinking, smoking, educational level, physical exercise, CVD family history, use of antidiabetic medication, and use of antihypertensive medication, ln(FBG), ln(TG), ln(hs-CRP), and ln(eGFR). [a] Baseline missing covariate data were not imputed ($n = 7564$). [b] Population that was followed up less than 1 years was excluded ($n = 561$). [c] Population who took antihypertensive medication was excluded ($n = 8990$). [d] Population who took antidiabetic medication was excluded ($n = 1920$). The association remained consistent across four sensitivity analyses, indicating the robustness of the association between RC/HDL-C levels and ASCVD risk. Incidence densities and adjusted HRs were similar across subgroups

Table 3 Prediction performance of RC/HDL-C

Models	C-index (95% CI)	NRI (95% CI)	*P*-NRI	IDI (95% CI)	*P*-IDI
China-PAR model	0.7217 (0.7168, 0.7266)	-			
Model 1	0.7220 (0.7171, 0.7269)	0.0236 (0.0010, 0.0461)	0.0404	0.0001 (0.0001, 0.0002)	0.078
Model 2	0.7219 (0.7170, 0.7268)	0.0670 (0.0445, 0.0895)	< 0.001	0.0007 (0.0000, 0.0002)	0.120

Remnant cholesterol (RC), high density lipoprotein cholesterol (HDL-C), confidence interval (CI), concordance index (C-index), net reclassification improvement (NRI), integrated discrimination improvement (IDI), China-Prediction for Atherosclerotic Cardiovascular Disease Risk (China-PAR)

China-PAR model: ln(age), ln(SBP), ln(HDL-C), ln(TC), ln(WC), ln(BMI), smoking, diabetes, family history of CVD

Model 1: based China-PAR model, additional adjusted RC/HDL-C

Model 2: based China-PAR model, additional adjusted RC/HDL-C*ln(age)

this process was associated with inflammation, triggering the release of inflammatory factors that eventually lead to disease [36].

This is the first study to verify the long-term effect of RC/HDL-C ratio on ASCVD in China. Secondly, this study was based on the large population and long follow-up Kailuan cohort, and the sample selected was representative. Finally, biennial follow-up data were used to account for time-dependent variables, which further increased the reliability of the conclusions.

This study had several limitations. First, behavioral habits were not considered as time-dependent variables in the multivariable adjustment models, as these behaviors were self-reported, and therefore baseline information was used for adjustment in the models. And both MI and CI are core components of ASCVD, other clinical manifestations such as angina pectoris and peripheral artery disease were not included due to incomplete in the Kailuan cohort [25]. As a result, the overall burden of ASCVD may have been underestimated. Second, the diagnostic criteria for diabetes did not include glycated hemoglobin A1c (HbA1c) or 2-hour postprandial glucose (2hPP) [20], as these measurements were not available during the initial phase of the cohort (2006). Third, the participants' baseline age was 51.90 ± 12.68 years, so caution is needed when extrapolating the findings to younger populations. Fourth, while differences in HR values after multivariable adjustments were noted, further exploration using the Directed Acyclic Graph method in

epidemiology could provide deeper insights, though this was not implemented [37].

Conclusion

This study found that elevated RC/HDL-C levels increased the risk of ASCVD, as well as the risk of CI and MI. For each unit increase in RC/HDL-C, the risk of ASCVD increased by 12%. In the clinical primary prevention of ASCVD, paying attention to RC/HDL-C ratio can effectively determine the high-risk population. Taking timely treatment for dyslipidemia, especially dyslipidemia other than high LDL-C, which can effectively reduce the occurrence of ASCVD.

Supplementary Information

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Supplementary Material 1

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Author contributions

Yizhen TAN collected data and drafted the manuscript. Shuohua CHEN and Zhe HUANG contributed to the design of the study and analyzed data. Xiangfeng LU and Jianxin LI provided supervision and guidance for the research process. Youxin WANG provided the funding acquisition. Shouling WU provided the Kailuan data resources. Yun LI, Yuntao WU, and Ying WU conceptualized and designed the study, interpreted the data, and critically revised the manuscript for intellectual content.

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Data availability

Data generated or analyzed during this study are not publicly available due to confidentiality agreements with research collaborators but are available from the corresponding author upon reasonable request.

Declarations

Human ethics and consent to participate

All participants were fully aware of the study protocol and signed informed consent forms. This study was reviewed by the Ethics Committee of Kailuan General Hospital (2006-05).

Competing interests

The authors declare no competing interests.

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