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ORIGINAL RESEARCH

Separate and Joint Associations of Remnant Cholesterol Accumulation and Variability With Carotid Atherosclerosis: A Prospective Cohort Study

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BACKGROUND: We aimed to examine separate and joint associations of remnant cholesterol (RC) accumulation and variability with the risk of carotid atherosclerosis (CAS) in the general population.

METHODS AND RESULTS: A total of 6213 participants who underwent 3 sequential health examinations during 2010 to 2015 were enrolled and were followed up until December 31, 2021. Cumulative RC (cumRC) and RC variability among the 3 visits were the exposure of interest in our study. Adjusted Cox models were performed to calculate the hazard ratio (HR) and 95% CI. C-statistics, integrated discrimination improvement, and the net reclassification index were used to estimate the incremental predictive ability. During a median follow-up of 4.00 years, 2613 participants developed CAS. Higher cumRC (HR, 1.33 [95% CI, 1.17–1.52]) and greater RC variability (HR, 1.22 [95% CI, 1.08–1.39]) were significantly associated with elevated risk of CAS, independent of traditional cardiovascular risk factors and low-density lipoprotein cholesterol. Participants were divided into 4 groups according to the median of cumRC and RC variability to assess their joint associations. Compared with "low cumRC and low variability," "high cumRC and high variability" had the highest risk of CAS, followed by "high cumRC and low variability" and "low cumRC and high variability." Finally, joint assessment of RC accumulation and variability had the significantly highest incremental effect on the predictive value of CAS versus single-time-point measures of RC.

CONCLUSIONS: Excessive cumRC levels and greater RC variability were each independently associated with higher incidence of CAS, and their coexistence could further yield significantly higher risks.

Key Words: carotid atherosclerosis ■ cohort study ■ cumulative exposure ■ remnant cholesterol ■ visit-to-visit variability

Cardiovascular diseases (CVDs) have become one of the greatest threats to global public health and the leading cause of death in China.[1,2] Atherosclerosis is widely considered as the key pathological process in the development of CVD. Abnormal carotid intima-media thickness (CIMT) and the presence of carotid plaque (CP), as the simple and noninvasive ultrasound markers to identify carotid atherosclerosis (CAS), have been verified as strong and independent predictors of cardiovascular events and death.[3–6] Thus, early identification of possible risk factors of CAS has important implications for the primary prevention of CVD.

Dyslipidemia is a pivotal contributor to atherosclerosis and atherosclerotic CVD.[2] Among them, lowering low-density lipoprotein cholesterol (LDL-C), primarily through statin therapy, is the well-established therapy

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CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrated that higher cumulative remnant cholesterol levels and greater visit-to-visit variability of remnant cholesterol were each significantly associated with an elevated risk of carotid atherosclerosis, regardless of traditional cardiovascular risk factors, low-density lipoprotein cholesterol, and triglyceride levels.
- The coexistence of higher remnant cholesterol accumulation and variability could further exacerbate the independent risk of carotid atherosclerosis in the general population and have a significantly higher incremental effect on the predictive value of carotid atherosclerosis.

What Are the Clinical Implications?

- Treatment strategies to reduce remnant cholesterol accumulation and its fluctuations might have the potential to prevent atherosclerosis-related diseases.
- Joint assessment of remnant cholesterol accumulation and variability may be useful for the risk stratification and primary prevention of atherosclerotic cardiovascular disease, even in people with optimal low-density lipoprotein cholesterol level.

Nonstandard Abbreviations and Acronyms

BHMC	Beijing Health Management Cohort
CAS	carotid atherosclerosis
CIMT	carotid intima-media thickness
CP	carotid plaque
cumRC	cumulative remnant cholesterol
RC	remnant cholesterol
SV	successive variation

target and strategy for primary and secondary prevention of atherosclerotic diseases.[7,8] Nevertheless, patients with a substantial reduction in LDL-C still have a considerable residual risk of cardiovascular adverse events.[9,10] Some emerging evidence indicates that remnant cholesterol (RC) may explain this residual risk to a certain extent.[9–11] RC represents the cholesterol content of triglyceride-rich lipoproteins, composed of intermediate-density lipoprotein and very-low-density lipoprotein in the fasting state, and in the nonfasting state with extra chylomicron remnants.[11,12] RC is more abundant, bulky, and carries more cholesterol than LDL-C particles, it may be trapped and accumulated on the arterial wall more easily, and thus may become more atherogenic.[13,14] Several epidemiological studies attested that RC levels are significantly associated with CIMT, CP, and coronary atherosclerotic plaque, even in those with optimal LDL-C levels.[15–19] However, all of these previous studies were limited due to the cross-sectional design or lack of representativeness of study populations. Longitudinal associations between RC and risk of CAS in the general population are understudied.

Moreover, most of the prior studies only considered the baseline RC level at a single time point, failing to reflect its long-term cumulative exposure and longitudinal variation. To our knowledge, no study has explored the effect of RC accumulation over the years on atherosclerosis-related diseases. In addition, intra-individual visit-to-visit variability of cardiovascular risk factors has also been considered as an independent predictor of death and cardiovascular events, attracting a great deal of attention.[20,21] A recent study reported that greater RC variability was associated with ischemic stroke.[12] However, whether variability in RC levels can affect the incidence of CAS warrants further clarifications. Beyond that, we also reasoned that RC variability could modify the impact of RC accumulation on CAS, that is, there may be a joint effect between them.

Therefore, based on a prospective population-based cohort study, we aimed to investigate the separate and joint associations of cumulative RC (cumRC) and RC variability with the subsequent risk of CAS and assess their predictive value for CAS.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

The BHMC (Beijing Health Management Cohort) study is an ongoing prospective cohort study conducted in Beijing, China, recruiting participants to undergo comprehensive regular physical examinations in the 2 biggest health examination centers in Beijing. The ultrasonographic examination of the carotid arteries was included in the uniform physical examination package in addition to face-to-face questionnaire survey, physical measurement (height, weight, blood pressure, ultrasound, etc), and blood test. BHMC aims to investigate the risk factors and biomarkers of the multiple chronic diseases, therefore promoting the prevention, treatment, and management of chronic diseases.[22–24] This study was approved by the Ethics Committee of

Capital Medical University (grant number: 2020SY031). All participants provided written informed consent before taking part in this study.

Baseline visit was defined as the point of visit 1 between 2010 and 2011. Then, the health examination during 2012 to 2013 was defined as visit 2 and 2014 to 2015 as visit 3, correspondingly. We calculated RC accumulation and variability using RC levels in visit 1, visit 2, and visit 3 surveys to explore separate and joint effects of them on CAS after 2015. Six follow-up visits for information about carotid artery color Doppler ultrasonography were performed in 2016, 2017, 2018, 2019, 2020, and 2021. The timeline of the study is presented in Figure S1. Of 17 221 participants who attended health examinations including carotid artery ultrasonography measurement from 2010 to 2011 at baseline survey, 16 413 participants had completed 3 sequential health examinations from visit 1 to visit 3. To minimize the possible effect of reverse causality, 9841 participants with carotid atherosclerosis in or before 2015 were excluded. Then, a total of 157 participants without information on RC, and 202 participants diagnosed with cardiovascular or cerebrovascular disease, malignant tumor were further excluded. Finally, a total of 6213 participants were enrolled for the analyses (Figure S2). They were annually followed until December 31, 2021.

In our study population, 3976 participants had detailed information about the plaque morphology to determine the vulnerable CP within the follow-up period.

Measurements of RC, cumRC, and RC Variability

Blood samples were collected after an 8- to 12-hour overnight fasting period. Fasting blood samples were stored and measured in the central laboratory of Beijing Xiaotangshan Examination Center or Beijing Physical Examination Center in the same way. Total cholesterol, triglyceride, high-density lipoprotein cholesterol, and LDL-C were directly measured using the Olympus Automatic Biochemical Analyzer (Hitachi 747; Tokyo, Japan). RC was estimated as fasting total cholesterol minus LDL-C minus high-density lipoprotein cholesterol.[10] RC accumulation and variability among 3 visits from 2010 to 2015 were the exposure of interest in our study.

Indices of RC accumulation include cumRC, cumRC burden, and high-RC exposure duration. CumRC was calculated as the summed average RC levels for each pair of consecutive visits multiplied by the time interval between these 2 consecutive visits in years[25,26]:

$$\text{cumRC} = \left(\frac{\text{RC}_1 + \text{RC}_2}{2}\right) \times \text{time}_{1-2} + \left(\frac{\text{RC}_2 + \text{RC}_3}{2}\right) \times \text{time}_{2-3}$$

where RC_1, RC_2, and RC_3 indicate RC levels at the baseline, second, and third visits, and time_{1-2} and time_{2-3} indicate the time intervals between consecutive visits in years. Other cumulative indices were conducted to test the robustness of the results. CumRC burden was calculated as the weighted sum of the difference between the average RC levels for each pair of consecutive examinations and the clinical cutoff value[26]:

$$\text{cumRC burden} = \left(\frac{\text{RC}_1 + \text{RC}_2}{2} - \text{cutoff}\right) \times \text{time}_{1-2} + \left(\frac{\text{RC}_2 + \text{RC}_3}{2} - \text{cutoff}\right) \times \text{time}_{2-3}$$

The cutoff value for RC was determined using equivalent population percentiles from our study cohort corresponding to cut point for high LDL-C (130 mg/dL),[10] and its cutoff value is 28 mg/dL. If the values of the cumulative burdens between 2 consecutive visits were <0, this value would be considered as 0. High-RC exposure duration was defined as the times of visits with higher RC levels (>28 mg/dL) among the 3 visits, quantified as 0 years (never had high RC), 2 years (had high RC once), 4 years (had high RC twice), and 6 years (had high RC thrice).[26,27]

RC variability was assessed using 5 indices: (1) successive variation (SV, calculated as the square root of the average squared difference between successive measurements[28]); (2) variability independent of the mean (calculated as SD/[mean to the power of χ] and multiplied by 100, where χ is the regression coefficient on the basis of a natural logarithm of SD on the natural logarithm of the mean, obtained by nonlinear regression analysis in the PROC NLIN procedure of the SAS package[29]); (3) average real variability (calculated as the average absolute difference between successive measurements[28]); (4) SD; and (5) coefficient of variation (calculated as SD/mean×100%). Unlike SD, SV and average real variability take the order of measurements into account, and variability independent of the mean and coefficient of variation can minimize the correlation between the measurement of variability and the mean value.[12] We further stratified cumRC and RC variability into 4 categories according to quartiles. The lowest quartile was used as the reference category in the subsequent analyses.

To explore whether the association between RC variability and risk of CAS differed by the rise or fall in RC, we defined the direction of RC variability according to the previous study.[30] First, participants were divided into 2 groups on the basis of the median of RC variability to reflect stable and large variation. Next, a large fall and rise of RC were defined as decreased and increased RC in the large variation group, respectively.

Outcome

CAS was evaluated by the presence of CP or abnormal CIMT. Participants were placed in a supine position with mild neck extension. Carotid artery color Doppler ultrasonography was performed using a high-resolution ultrasonography system (iU-22 ultrasound system; Philips Medical Systems, Bothell, WA) with a 5- to 12-MHz linear array transducer by experienced radiologists. Their examination results were regularly assessed for consistency. Consistency assessments were performed every 3 months on average. All agreement rates exceeded 95%, with the highest being 99.5%. To reduce the variability of the cardiac cycle, diastolic images were recorded on all ultrasound images.[23] The distance from the echo front of the lumen intima to the echo front of the media adventitia was quantified as CIMT.[31] CIMT was measured at 4 sites (right, left, near walls, and far walls) for the common carotid arteries, internal carotid artery, and carotid bifurcations according to a standardized protocol.[23,31] The maximum CIMT of different carotid segments was used, and abnormal CIMT was defined as CIMT ≥1.0 mm.[32] Plaques were defined as focal structures encroaching into the arterial lumen of at least 0.5 mm, 50% of the surrounding CIMT value, or demonstrating a thickness >1.5 mm as measured from the intima–lumen interface to the media-adventitia interface.[31] CP was used as the secondary outcome.

Vulnerable CP was defined as an anechogenic or heterogeneous plaque, or a plaque with irregular or ulcerative surface.[33,34] This outcome was used in sensitivity analyses.

Assessment of Covariates

The demographic characteristics, health-related lifestyle, self-reported past medical history, and medication history were obtained using structured questionnaires by medically trained staff, including age; sex (male and female); current smoking status ("current smoking" and "no current smoking"); drinking status ("current drinking" and "no current drinking"); physical activity; andself-reported diagnosis and medication history of hypertension, diabetes, and dyslipidemia. Physical activity was defined as having moderate or intense exercise "≥20 minutes per time and ≥4 times per week."[22] Physical examination and blood test data were collected from the medical record system. Body mass index was calculated as weight (kg)/height $(m)^2$. Systolic blood pressure and diastolic blood pressure were presented as the average of 2 measurements using a standard mercury sphygmomanometer after resting for at least 10 minutes. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, use of any antihypertension medication, or self-reported diagnosis of hypertension.[35] The data of fasting blood glucose, glycated hemoglobin, serum uric acid, serum creatinine, and postprandial blood glucose were also collected in this current study. type 2 diabetes was defined as fasting blood glucose ≥7.0 mmoL/L, postprandial blood glucose ≥11.1 mmoL/L, glycated hemoglobin ≥6.5%, use of any glucose-lowering medication, or self-reported diagnosis of type 2 diabetes.[23] We calculated the estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration's 2009 creatinine equation.[36]

Statistical Analysis

Baseline characteristics were presented as the mean (SD), median (interquartile range), or number (percentage). Differences between groups were compared using the chi-square test or Fisher's exact test for categorical variables, and 1-way ANOVA test or Kruskal–Wallis test for continuous variables, as appropriate.

The Cox proportional hazards models were used to investigate the associations of cumulative RC and RC variability with the risk of incident CAS and CP. The hazard ratio (HR) and 95% CI were obtained. To adjust for potential confounding factors, model 1 was adjusted by age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, and estimated glomerular filtration rate. Model 2 was additionally adjusted by LDL-C to explore whether the observed associations were independent of LDL-C. When RC variability was the main exposure, we further adjusted for cumRC in models 1 and 2. We evaluated the dose–response relationship of both cumRC and RC variability, as continuous change, with CAS and CP using restricted cubic splines with 3 knots (at the 10th, 50th, and 90th percentiles), adjusting for the same variables as in the Cox regression analyses. For the direction of RC variability, fully adjusted models were used to assess the association between large rise or fall in RC and the risk of CAS or CP, with stable RC as the reference.

Using the same models, we assessed the joint associations of cumRC and RC variability with the risk of CAS. Participants were divided into 4 combined groups, according to the median of cumRC and RC variability (greater than or equal to the median and less than the median): "low cumRC and low variability," "low cumRC and high variability," "high cumRC and low variability," and "high cumRC and high variability." Our reference group was the "low cumRC and low variability" group. We also used cumRC burden (burden >0 and burden=0) as cut points for high and low cumRC to redefine the 4 groups and to assess the robustness

of our findings. Furthermore, participants were further stratified into 8 groups on the basis of their cumulative burden of LDL-C, to further clarify whether the association of combination of RC accumulation and variability with CAS would be altered by LDL-C levels. The calculation formula of cumulative LDL-C burden is the same as that of cumRC burden, and 130 mg/dL was chosen as the cut point for high LDL-C.[10]

We conducted multiple sensitivity analyses. First, we repeated our analyses adjusting for cumulative triglyceride rather than LDL-C to elucidate whether cumRC and RC variability remain the risk factors independent of circulating triglyceride levels. To compare the atherogenic effects of RC versus triglyceride, we also individually modeled the associations of cumulative triglyceride with risk of CAS and included both cumulative triglyceride and RC in the same multivariable-adjusted model. Second, in the physical examination information database, continuous CIMT values were recorded for participants with CAS. Thus, among individuals with specific and continuous CIMT values, multivariate linear regression models were used to estimate the longitudinal association of the baseline cumRC and RC variability with the continuous CIMT at the final follow-up visit, further adjusted for the follow-up duration. Third, we repeated the analysis in people without the use of lipid-lowering medications. Fourth, to minimize reverse causality, participants diagnosed with CAS that occurred within the first year of follow-up were excluded. Finally, we assessed the associations of RC accumulation and variability with the incidence of vulnerable CP.

Finally, we used C-statistics, integrated discrimination improvement, and continuous net reclassification index to compare the incremental predictive value of cumRC, RC variability, and their combined effect beyond other conventional risk factors and baseline RC at a single time point.

Two-sided $P<0.05$ was considered as statistically significant. All statistical analyses above were performed with R software version 4.1.0 and SAS statistical software Version 9.4 (SAS Institute Inc. Cary, NC).

RESULTS

Baseline Characteristics

Of the 6213 participants, 3323 (53.5%) were men, and the median (interquartile range) age of the population was 46.00 (41.00–52.00) years. During a median follow-up of 4.00 (95% CI, 3.98–4.01) years, 2613 (42.1%) participants developed CAS and 1327 (21.4%) participants developed CP. Table 1 shows the baseline characteristics of the study population by combination of cumRC and RC variability (measured by SV). Participants in the "high cumRC and high variability" group tended to have a higher incidence rate of CAS and CP ($P<0.001$). The baseline characteristics of population according to quartiles of cumRC and RC variability, as measured by SV, are shown in Tables S1 and S2.

Associations Between Cumulative RC and Incident Carotid Atherosclerosis

The relationships between cumulative RC parameters and the incidence of CAS are presented in Table 2. In model 1, participants in quartile 4 of cumRC had a higher risk of CAS (HR, 1.33 [95% CI, 1.17–1.52]) and CP (HR, 1.78 [95% CI, 1.47–2.15]) compared with those in quartile 1 of cumRC. This association remained significant after adjusting LDL-C in the model. Additionally, similar results were observed for cumulative burden of RC and high-RC exposure duration. Those with cumRC burden >0 or longer high-RC exposure duration had elevated risks of developing CAS and CP. Finally, multivariable-adjusted restricted cubic spline models showed a J-shaped dose–response relationship of cumRC with CAS and CP risk (Figure 1A and 1C).

Associations Between RC Variability and Incident Carotid Atherosclerosis

Table 3 summarizes the associations between each RC variability index and the risk of CAS. After adjusting for cumRC in addition to several traditional cardiovascular risk factors in model 1, participants with quartile 4 of SV had 1.22-fold higher risk of CAS (HR, 1.22 [95% CI, 1.08–1.39]) and 1.40-fold higher risk of CP (HR, 1.40 [95% CI, 1.17–1.67]) compared with the lowest quartile of SV. The associations persisted after further adjustment for LDL-C, with HRs of 1.16 (95% CI, 1.02–1.31) for CAS and 1.31 (95% CI, 1.09–1.56) for CP. Likewise, RC variability as captured by variability independent of the mean, average real variability, SD, or coefficient of variation remained strongly associated with CAS and CP. Furthermore, the dose–response relationship for RC variability also confirmed that higher variability significantly increased the risk of CAS and CP (Figure 1B and 1D).

After accounting for the direction of RC variability (Table S3), we found the associations of RC variability with risk of CAS and CP was irrespective of RC variability direction. Both a large fall and rise in RC were all correlated to elevated risk of CAS and CP, compared with the stable RC group.

Joint Associations of cumRC and RC Variability With Carotid Atherosclerosis

When considering the combined effect of RC accumulation and variability, the HRs for each group on the basis of median of cumRC and RC variability are shown

Table 1. Baseline Characteristics of the Study Population According to Combination of cumRC and RC Variability (Measured by SV)

Characteristics	Overall (n=6213)	Low cumRC, low variability (n=2268)	Low cumRC, high variability (n=838)	High cumRC, low variability (n=838)	High cumRC, high variability (n=2269)
Age, y	46.00 (41.00–52.00)	45.00 (40.00–51.00)	45.00 (40.00–51.75)	48.00 (42.00–53.00)	47.00 (41.00–53.00)
Male, n (%)	3323 (53.5)	825 (36.4)	380 (45.3)	549 (65.5)	1569 (69.1)
BMI, kg/m^2	24.45 (22.34–26.78)	22.91 (21.01–24.88)	23.8 (21.85–25.87)	25.51 (23.44–27.96)	25.72 (23.83–27.89)
Hypertension, n (%)	2268 (36.5)	499 (22)	248 (29.6)	371 (44.3)	1150 (50.7)
Diabetes, n (%)	664 (10.7)	119 (5.2)	69 (8.2)	98 (11.7)	378 (16.7)
SBP, mm Hg	120.00 (110.00–129.00)	110.00 (103.00–120.00)	115.00 (108.00–125.00)	120.00 (110.00–130.00)	120.00 (110.00–130.00)
DBP, mm Hg	77.00 (70.00–82.00)	70.00 (66.00–80.00)	74.00 (69.00–80.00)	80.00 (70.00–85.00)	80.00 (70.00–88.00)
Fasting blood glucose, mmol/L	5.24 (4.93–5.62)	5.10 (4.82–5.41)	5.18 (4.92–5.49)	5.32 (5.00–5.72)	5.38 (5.06–5.84)
SUA, μmol/L	307.80 (246.90–374.85)	263.32 (218.97–320.78)	281.20 (231.01–339.32)	341.85 (285.81–402.06)	349.30 (289.70–411.48)
eGFR, mL/min per 1.73 m^2	104.57 (95.60–111.77)	106.59 (96.69–113.56)	106.20 (97.03–113.37)	101.55 (93.60–108.83)	103.34 (94.81–109.90)
Lipid-lowering medication use, n (%)	166 (2.7)	23 (1.0)	15 (1.8)	30 (3.6)	98 (4.3)
Current smoker, n (%)	1605 (25.8)	446 (19.7)	184 (22.0)	234 (27.9)	741 (32.7)
Current drinker, n (%)	2453 (39.5)	762 (33.6)	319 (38.1)	373 (44.5)	999 (44.0)
Active physical activity, n (%)	2679 (43.1)	911 (40.2)	369 (44.0)	378 (45.1)	1021 (45.0)
RC variability					
SV, mg/dL	4.19 (2.32–7.30)	2.17 (1.35–3.06)	5.64 (4.84–6.88)	2.76 (1.79–3.44)	8.61 (6.14–13.40)
VIM	4.13 (2.53–6.11)	3.06 (1.97–4.31)	6.82 (5.62–8.32)	1.88 (1.29–2.65)	5.36 (3.93–7.29)
ARV, mg/dL	3.76 (2.10–6.70)	1.94 (1.22–2.71)	5.11 (4.36–6.37)	2.46 (1.60–3.08)	7.73 (5.52–12.36)
SD, mg/dL	3.12 (1.72–5.42)	1.62 (1.02–2.27)	4.10 (3.37–4.97)	2.04 (1.38–2.66)	6.25 (4.58–9.49)
CV	15.12 (9.00–22.53)	9.96 (6.36–13.85)	22.96 (18.87–27.78)	7.42 (5.11–10.17)	21.79 (16.35–30.34)
Cumulative lipid level					
Cumulative RC, mg/dL×year	84.58 (66.73–112.68)	64.21 (57.35–72.57)	73.45 (66.70–79.36)	100.31 (91.89–116.69)	118.97 (99.99–151.91)
Cumulative triglyceride, mg/dL×year	437.68 (305.67–660.96)	287.06 (232.13–343.77)	356.17 (304.12–396.93)	565.71 (489.07–698.83)	711.46 (557.29–1005.61)
Cumulative LDL-C, mg/dL×year	436.94 (366.73–506.45)	404.38 (346.35–465.85)	427.00 (362.24–482.86)	473.20 (409.41–544.24)	463.53 (390.47–534.28)
Cumulative HDL-C, mg/dL×year	201.03 (171.26–235.05)	227.13 (199.49–259.41)	216.88 (188.66–246.94)	186.34 (160.05–210.21)	177.45 (156.57–203.35)
Cumulative TC, mg/dL×year	736.09 (660.70–823.46)	698.30 (628.22–767.40)	712.50 (644.46–789.73)	763.34 (684.38–848.49)	783.25 (705.55–869.46)
Cumulative burden of RC >0, n (%)	1849 (29.8)	0 (0.0)	1 (0.1)	294 (35.1)	1554 (68.5)
Exposure duration of high-RC*, n (%)					
0 y	3877 (62.4)	2268 (100.0)	783 (93.4)	482 (57.5)	344 (15.2)
2 y	853 (13.7)	0 (0.0)	55 (6.6)	107 (12.8)	691 (30.5)
4 y	642 (10.3)	0 (0.0)	0 (0.0)	72 (8.6)	570 (25.1)
6 y	841 (13.5)	0 (0.0)	0 (0.0)	177 (21.1)	664 (29.3)
Outcomes					
Carotid atherosclerosis, n (%)	2613 (42.1)	792 (34.9)	324 (38.7)	406 (48.4)	1091 (48.1)
Carotid plaque, n (%)	1327 (21.4)	340 (15.0)	164 (19.6)	209 (24.9)	614 (27.1)

Data are presented as the mean (SD), median (IQR), or number (%), as appropriate. ARV indicates average real variability; BMI, body mass index; cumRC, cumulative remnant cholesterol; CV, coefficient of variation; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; SBP, systolic blood pressure; SUA, serum uric acid; SV, successive variation; TC, total cholesterol; and VIM, variability independent of the mean.

*High RC was defined as RC levels >28 mg/dL.

Table 2. Associations Between Cumulative Remnant Cholesterol Indexes and the Incidence of Carotid Atherosclerosis and Carotid Plaque

	Carotid atherosclerosis, HR (95% CI)		Carotid plaque, HR (95% CI)	
	Model 1	Model 2	Model 1	Model 2
cumRC, mg/dL×year				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.18 (1.04–1.33)	1.05 (0.93–1.19)	1.40 (1.17–1.68)	1.23 (1.03–1.48)
Quartile 3	1.33 (1.18–1.51)	1.14 (1.01–1.30)	1.58 (1.32–1.90)	1.32 (1.09–1.59)
Quartile 4	1.33 (1.17–1.52)	1.16 (1.01–1.32)	1.78 (1.47–2.15)	1.50 (1.23–1.82)
Cumulative burden of RC				
=0	Reference	Reference	Reference	Reference
>0	1.13 (1.03–1.23)	1.06 (0.97–1.16)	1.19 (1.06–1.35)	1.16 (1.03–1.31)
Exposure duration of high RC*				
0 y	Reference	Reference	Reference	Reference
2 y	1.14 (1.02–1.28)	1.08 (0.97–1.22)	1.23 (1.05–1.44)	1.14 (0.97–1.33)
4 y	1.14 (1.00–1.30)	1.06 (0.93–1.20)	1.41 (1.19–1.67)	1.31 (1.11–1.56)
6 y	1.18 (1.04–1.33)	1.11 (0.99–1.26)	1.35 (1.15–1.59)	1.26 (1.07–1.48)

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol. cumRC indicates cumulative remnant cholesterol from visit 1 to visit 3 (2010–2015); HR, hazard ratio; and RC, remnant cholesterol.

*High-RC was defined as RC levels >28 mg/dL.

in Figure 2. In the fully adjusted model including LDL-C (model 2), participants in the "high cumRC and high SV" group had the highest risk of CAS (HR, 1.21 [95% CI, 1.09–1.34]), followed by participants in the "high cumRC and low SV" group (HR, 1.21 [95% CI, 1.06–1.37]) and "low cumRC and high SV" group (HR, 1.14 [95% CI, 1.00–1.30]). The results did not change materially after RC variability measured using variability independent of the mean, average real variability, SD, or coefficient of variation. Similar results were also observed in CP end point. As shown in Figure 3, the highest risk of CP was also found at the higher levels of both RC accumulation and variability in the both model 1 (HR, 1.51 [95% CI, 1.30–1.74]) and model 2 (HR, 1.41 [95% CI, 1.22–1.64]). After using the cut points of cumRC burden and median of RC variability and taking both cumRC burden=0 and low variability as the reference group, results were roughly consistent with the main analyses (Figures S3 and S4). It should be noted that the insignificance of HRs for "burden>0 and low variability" could have been due to the small sample size of this group.

In Table 4, when categorizing according to the cum-LDL-C burden, cumRC, and RC variability together, participants had higher levels of LDL, cumRC, and RC variability (as measured by SV) simultaneously had the significantly highest risk of CAS (HR, 1.60 [95% CI, 1.41–1.82]) and CP (HR, 2.03 [95% CI, 1.69–2.43]) compared with those with lower levels of them. Noticeably, high levels of cumRC alone, high levels of variability alone or combination of them still significantly related with the development of CAS and CP, among those without cumulative burden of LDL-C.

Sensitivity Analysis

First, adjusting for cumulative triglyceride rather than LDL-C in our multivariable models revealed that cumRC, RC variability, and their combination remained independently associated with risk of CAS and CP (Tables S4 and S5). As displayed in Table S6, we also indicated that higher cumulative triglyceride levels were associated with CAS (HR, 1.18 [95% CI, 1.03–1.34]) and CP (HR, 1.53 [95% CI, 1.26–1.85]) after adjusting for traditional cardiovascular risk factors and LDL-C. However, when cumulative triglyceride and cumRC were both included in the same multivariable-adjusted model, triglyceride was no longer associated with CAS (HR, 0.84 [95% CI, 0.58–1.22]) and CP (HR, 0.80 [95% CI, 0.47–1.35]). The risk for CAS and CP appears to be more strongly associated with cumRC than cumulative triglyceride.

Second, after a 6-year follow-up, it was observed that 2613 individuals had developed CAS, and the database recorded the continuous CIMT values at the final follow-up visit of these individuals. Further analysis using continuous CIMT levels as the outcome variable did not result in any significant changes in the findings (Tables S7 and S8). Those with elevated cumRC, greater RC variability, and their combination were more likely to have higher continuous CIMT values at the final follow-up visit. Additionally, we also observed consistent results when excluding individuals with lipid-lowering medication use (Tables S9 and S10) or excluding those with CAS that occurred within the first year of follow-up (Tables S11 and S12).

Finally, as demonstrated in Table S13, the positive association between the cumRC or RC variability and vulnerable CP remained significant across all adjusted

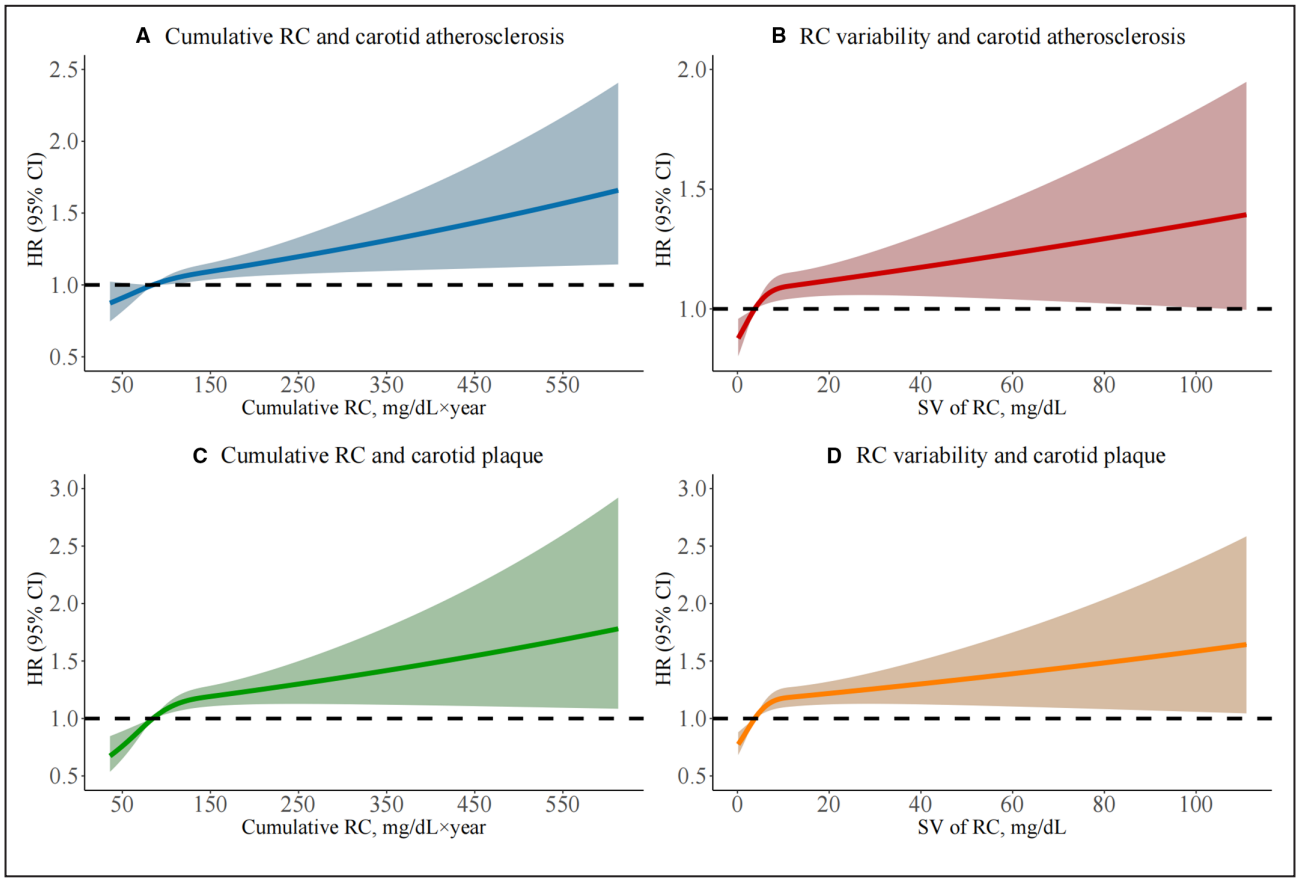

Figure 1. Dose–response relationship of baseline cumulative remnant cholesterol and remnant cholesterol variability with incidence of carotid atherosclerosis and carotid plaque.
A, Dose–response relationship between cumulative RC and carotid atherosclerosis. **B**, Dose–response relationship between RC variability and carotid atherosclerosis. **C**, Dose–response relationship between cumulative RC and carotid plaque. **D**, Dose–response relationship between RC variability and carotid plaque. The curve was estimated by restricted cubic spline function with 3 knots. Solid lines indicate HRs. The shadow represents 95% CIs. Adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate, and low-density lipoprotein cholesterol. HR indicates hazard ratio; RC, remnant cholesterol; and SV, successive variation.

models. In model 2, the HR value was 1.50 (95% CI, 1.06–2.12) for the highest quartile of cumRC and 1.37 (95% CI, 1.01–1.85) for the highest quartile of RC variability (as measured by SV), compared with the lowest quartile of them. The coexistence of high cumRC and high variability (as measured by SV) was significantly associated with the greatest risk of vulnerable CP than that of the reference group (low cumRC and low variability) (HR, 1.44 [95% CI, 1.13–1.85]). The associations of "low cumRC and high SV" or "high cumRC and low SV" with vulnerable CP were also significant in model 1. However, this association became borderline significant after further adjusting for LDL-C in model 2.

Incremental Predictive Value of Cumulative RC and RC Variability

We defined the model including traditional cardiovascular risk factors and RC measured at only a single time point as the reference predictive models of CAS and CP. Table 5 showed that using cumRC or combination of RC accumulation and variability instead of single-time-point measures of RC significantly improved the reclassification and discrimination ability compared with the reference model and yielded a modest but not significant increase in the C-statistic. The discriminatory power and risk reclassification of "cumRC+ variability" combination (net reclassification index, 0.1291; $P<0.0001$; integrated discrimination improvement, 0.0024; $P=0.0001$) appeared to be substantial better than cumRC alone (net reclassification index, 0.0643; $P=0.0113$; integrated discrimination improvement, 0.0013; $P=0.0055$). When we use the model containing cumRC as the reference model, the results further confirmed this conclusion that the addition of RC variability to the model including cumRC had a significantly higher incremental effect on the predictive value for incident CAS and CP. Conversely, the

Table 3. Associations Between Variability of Remnant Cholesterol and the Incidence of Carotid Atherosclerosis and Carotid Plaque

	Carotid atherosclerosis, HR (95% CI)		Carotid plaque, HR (95% CI)	
	Model 1	Model 2	Model 1	Model 2
SV				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.20 (1.07–1.34)	1.17 (1.04–1.31)	1.22 (1.03–1.45)	1.18 (0.99–1.40)
Quartile 3	1.21 (1.08–1.35)	1.13 (1.01–1.27)	1.37 (1.16–1.62)	1.27 (1.07–1.50)
Quartile 4	1.22 (1.08–1.39)	1.16 (1.02–1.31)	1.40 (1.17–1.67)	1.31 (1.09–1.56)
VIM				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.07 (0.94–1.22)	1.06 (0.93–1.21)	1.20 (1.03–1.40)	1.17 (1.00–1.37)
Quartile 3	1.17 (1.03–1.33)	1.16 (1.02–1.32)	1.14 (0.97–1.33)	1.13 (0.97–1.32)
Quartile 4	1.17 (1.03–1.33)	1.18 (1.04–1.35)	1.12 (0.96–1.31)	1.16 (0.99–1.36)
ARV				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.19 (1.06–1.34)	1.16 (1.04–1.30)	1.32 (1.11–1.56)	1.26 (1.06–1.49)
Quartile 3	1.22 (1.09–1.37)	1.14 (1.02–1.28)	1.41 (1.19–1.66)	1.30 (1.10–1.53)
Quartile 4	1.22 (1.07–1.38)	1.15 (1.02–1.31)	1.44 (1.21–1.73)	1.33 (1.12–1.60)
SD				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.20 (1.07–1.35)	1.16 (1.04–1.30)	1.28 (1.09–1.52)	1.23 (1.04–1.45)
Quartile 3	1.18 (1.05–1.32)	1.10 (0.98–1.23)	1.29 (1.09–1.52)	1.18 (1.00–1.40)
Quartile 4	1.22 (1.08–1.39)	1.15 (1.01–1.31)	1.40 (1.17–1.68)	1.30 (1.09–1.56)
CV				
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.09 (0.96–1.25)	1.08 (0.94–1.23)	1.15 (0.98–1.35)	1.11 (0.95–1.31)
Quartile 3	1.20 (1.06–1.37)	1.18 (1.03–1.34)	1.22 (1.05–1.43)	1.18 (1.01–1.39)
Quartile 4	1.21 (1.06–1.38)	1.20 (1.05–1.37)	1.18 (1.00–1.39)	1.18 (1.01–1.39)

Model 1: adjusted for cumulative remnant cholesterol, age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol. ARV indicates average real variability; CV, coefficient of variation; HR, hazard ratio; SV, successive variation; and VIM, variability independent of the mean.

prediction model including RC variability alone may not significantly improve the predictive power of conventional models.

DISCUSSION

To the best of our knowledge, this is the first prospective cohort study to explore the separate and joint associations of RC accumulation and variability with CAS. First, we found that elevated cumulative RC levels and long exposure duration of high RC were each significantly associated with incident CAS independent of traditional cardiovascular risk factors, LDL-C and triglyceride. Second, higher long-term variability of RC was related to increased risk of developing CAS, irrespective of the direction of RC variability. Third, we also confirmed our hypothesis that there may be joint or synergistic effects between cumRC and RC variability on CAS. Individuals with both higher cumRC and greater fluctuation of RC showed the highest risk for CAS. High RC variability alone also could enhance the risk significantly, even when the cumRC was at relatively low levels, and this association still holds among people under an optimal LDL-C level. Our finding was robust in multiple sensitivity analyses and the use of secondary outcomes (including CP and vulnerable CP). Finally, our findings also provided strong evidence that cumRC or combination of RC accumulation and variability had a significantly higher incremental effect on the predictive value of CAS versus single-time-point measures of RC, and the combination of the 2 showed the highest predictive value. These novel findings suggested that the combined evaluation of the long-term cumRC and RC variability may be a better strategy for primary prevention of CAS to counteract the development of atherosclerotic CVD.

Several prior studies have reported that RC is strongly correlated with incident ischemic stroke, CVD, and death.[10,37–41] However, the prospective evidence

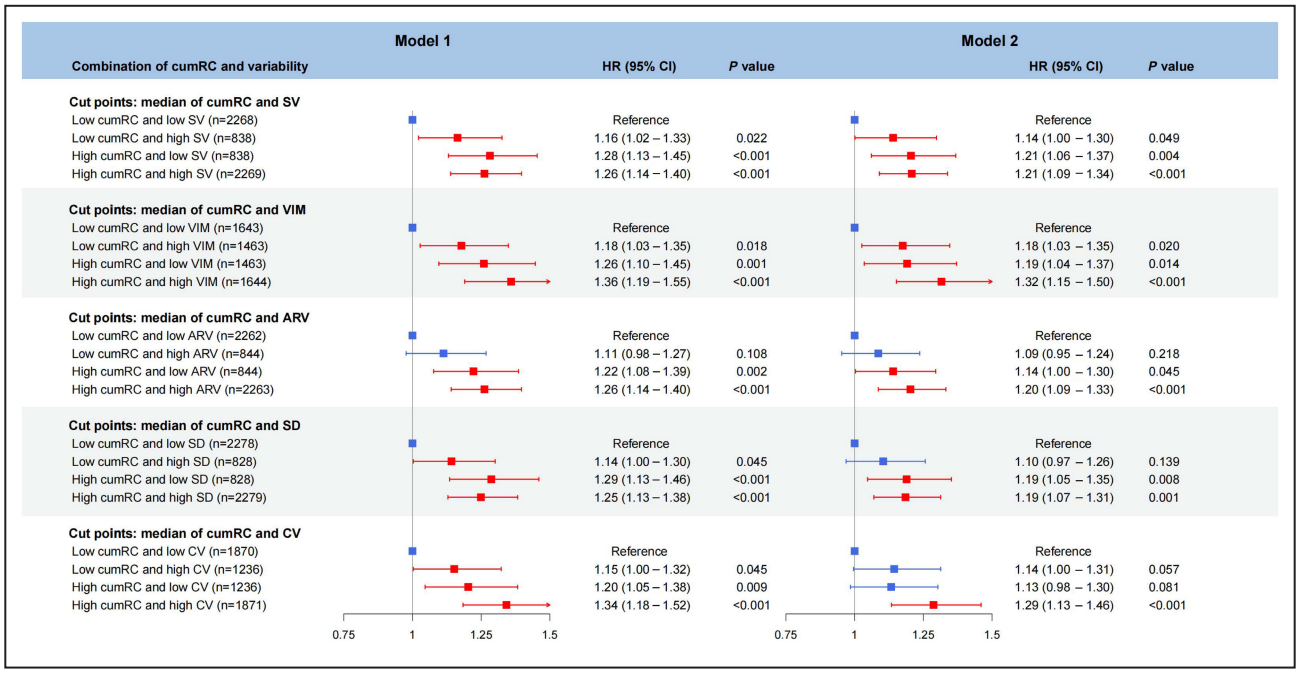

Figure 2. Joint associations of cumRC and RC variability with the incidence of carotid atherosclerosis after participants were divided into 4 combined groups according to the median of cumRC and RC variability.
Graphs show HR and 95% CIs for the incidence of carotid atherosclerosis in models 1 and 2. Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol. Red HR value is statistically significant; blue means HR value is not statistically significant. ARV indicates average real variability; CV, coefficient of variation; cumRC, cumulative remnant cholesterol; HR, hazard ratio; RC, remnant cholesterol; SV, successive variation; and VIM, variability independent of the mean.

of association between RC and CAS was limited. Two cross-sectional studies reported that elevated concentrations of RC were associated with abnormal CIMT among children and adolescents or patients with ischemic stroke, respectively.[16,19] Another study performed in 587 patients with suspected coronary artery disease revealed a significant relationship between RC and total coronary atherosclerotic plaque burden, and these associations remained in patients with optimal LDL-C level.[17] Our findings, based on a large, prospective cohort study, were in accordance with conclusions from the above studies and provided prospective evidence in the general population to further extend these prior studies. Moreover, previous studies have been reliant on a single-time-point measurement of RC, ignoring the fluctuation of RC over time, and were unable to reflect long-term, true exposure levels of RC. However, the natural history of atherosclerosis is prolonged. The development of CAS may be determined by cumulative exposure of RC. Based on this consideration, our study is the first to assess the relationship between cumRC and incident CAS. We contemplate that only long-term exposure to lower levels of RC could reduce the risk of onset of CAS. Another important finding was that cumRC provides an independent and incremental predictive value beyond the RC levels at a single time point, indicating that cumulative exposure value may offer more information for the risk stratification of atherosclerosis-related diseases.

Moreover, variability in various biological parameters has been recognized as a novel biomarker with important clinical significance. Our study provides the first evidence that RC variability is an independent marker of increased CAS risk irrespective of the direction of variability, and this association was independent of lipid-lowering medication use, cumulative RC, triglyceride, and LDL-C levels. The positive relationship between elevated RC variability and incident ischemic stroke in the general population has been well documented in the previous Kailuan study.[12] They inferred that greater RC fluctuations may render plaques more unstable and prone to rupture and eventually contribute to elevated ischemic stroke risk,[12]while our results confirmed this conjecture. Our findings suggest that elevated RC variability is a significant risk factor for the occurrence of asymptomatic vulnerable CP. Another recent study conducted in patients with type 2 diabetes suggested that subjects with higher RC variability also had an increased risk of major adverse cardiovascular events.[42] Thus, our results may provide a possible mechanism linking visit-to-visit fluctuation in RC and cardiovascular events or stroke via mediation of atherosclerosis or vulnerable CP.

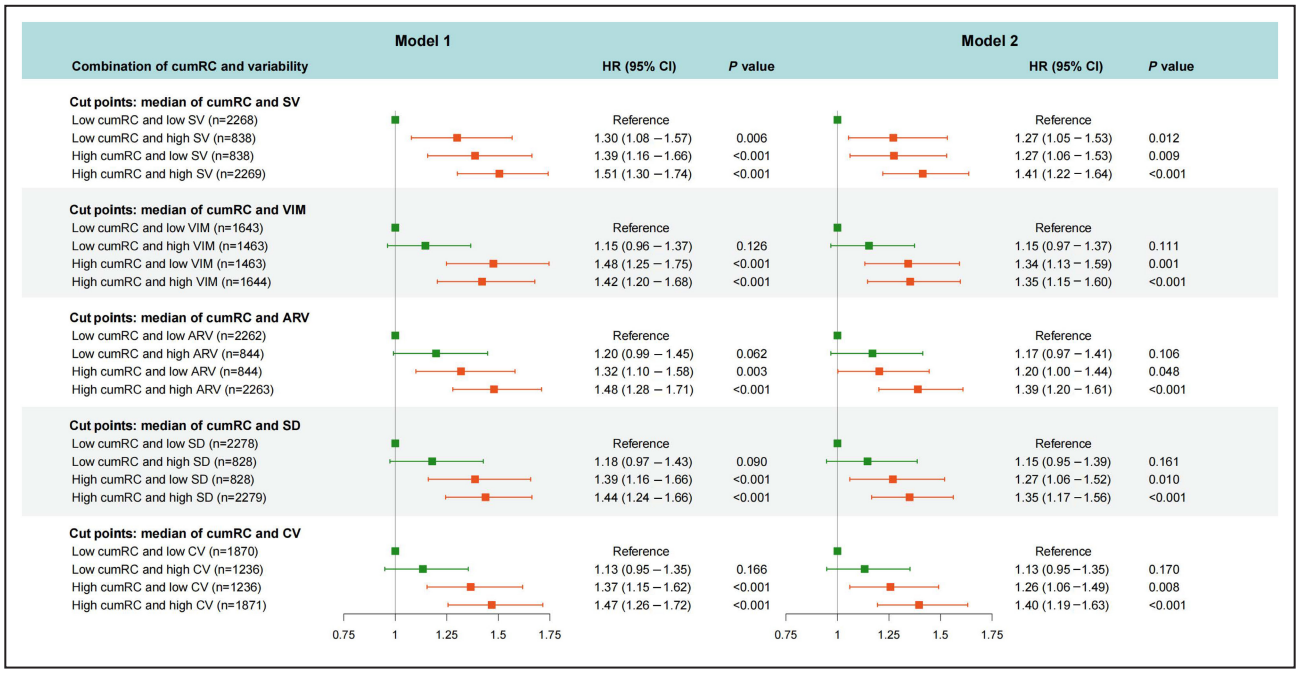

Figure 3. Joint associations of cumRC and RC variability with the incidence of carotid plaque after participants were divided into 4 combined groups according to the median of cumRC and RC variability.
Graphs show HR and 95% CIs for the incidence of carotid plaque in models 1 and 2. Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol. Orange means HR value is statistically significant; green means HR value is not statistically significant. ARV indicates average real variability; CV, coefficient of variation; cumRC, cumulative remnant cholesterol; HR, hazard ratio; RC, remnant cholesterol; SV, successive variation; and VIM, variability independent of the mean.

However, the exact mechanisms underlying the association of RC variability with CAS remain unclear. We propose several hypotheses. First, individuals who exhibit greater variability in blood lipid levels often accompanied with cardiovascular risk factors.[43] In our study, as shown in Table S2, baseline higher RC variability may also be observed in people with the presence of obesity, hypertension, diabetes, and the like, which were all closely related to atherosclerosis. Second, fluctuations in cholesterol levels may be detrimental to endothelium and lead to endothelial dysfunction, oxidative stress, and inflammation, all of which are important pathophysiological components of many diseases caused by metabolic dysfunction.[12,44,45] These factors could accelerate the advancement of atherosclerosis. Additionally, the dosing and adherence of lipid-lowering

Table 4. Joint Associations Between cumLDL-C Burden, cumRC, and RC Variability (Measured by SV) and the Incidence of Carotid Atherosclerosis and Carotid Plaque

	Carotid atherosclerosis		Carotid plaque	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
cumLDL-C burden=0, low cumRC, and low variability (n=1945)	Reference		Reference	
cumLDL-C burden=0, low cumRC, and high variability (n=692)	1.17 (1.01–1.35)	0.035	1.25 (1.01–1.55)	0.043
cumLDL-C burden=0, high cumRC, and low variability (n=527)	1.22 (1.05–1.42)	0.010	1.41 (1.13–1.75)	0.002
cumLDL-C burden=0, high cumRC, and high variability (n=1484)	1.18 (1.04–1.32)	0.007	1.49 (1.26–1.77)	<0.001
cumLDL-C burden >0, low cumRC and low variability (n=323)	1.28 (1.07–1.54)	0.008	1.50 (1.15–1.95)	0.003
cumLDL-C burden >0, low cumRC, and high variability (n=146)	1.40 (1.10–1.79)	0.007	2.18 (1.59–2.98)	<0.001
cumLDL-C burden >0, high cumRC, and low variability (n=311)	1.56 (1.31–1.86)	<0.001	1.71 (1.33–2.21)	<0.001
cumLDL-C burden >0, high cumRC, and high variability (n=785)	1.60 (1.41–1.82)	<0.001	2.03 (1.69–2.43)	<0.001

Model adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, and estimated glomerular filtration rate. cumRC indicates cumulative remnant cholesterol; cumLDL-C, cumulative low-density lipoprotein cholesterol; HR, hazard ratio; RC, remnant cholesterol; and SV, successive variation.

Table 5. Reclassification and Discrimination Statistics for Cumulative Remnant Cholesterol and Its Variability (Measured by SV)

Models	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value	C statistics (95% CI)	*P* value
Outcome: carotid atherosclerosis						
Model*+RC (single time point)	Reference		Reference		0.7104 (0.6977 to 0.7231)	-
Model*+cumRC	0.0643 (0.0145 to 0.1141)	0.0113†	0.0013 (0.0004 to 0.0023)	0.0055†	0.7114 (0.6987 to 0.7241)	0.1997
Model*+RC variability	0.0577 (0.0073 to 0.1080)	0.0247†	0.0010 (–0.0003 to 0.0023)	0.1154	0.7115 (0.6988 to 0.7242)	0.3171
Model*+cumRC+RC variability	0.1291 (0.0793 to 0.1789)	<0.0001†	0.0024 (0.0012 to 0.0037)	0.0001†	0.7122 (0.6995 to 0.7249)	0.0832
Change reference model						
Model*+cumRC	Reference		Reference		0.7114 (0.6987 to 0.7241)	-
Model*+cumRC+RC variability	0.1073 (0.0612 to 0.1534)	<0.0001†	0.0011 (0.0003 to 0.0019)	0.0010†	0.7122 (0.6995 to 0.7249)	0.2794
Outcome: carotid plaque						
Model*+RC (single time point)	Reference		Reference		0.6920 (0.6768 to 0.7072)	-
Model*+cumRC	0.1270 (0.0664 to 0.1875)	<0.0001†	0.0015 (0.0004 to 0.0025)	0.0055†	0.6930 (0.6778 to 0.7082)	0.4335
Model*+RC variability	–0.0047 (–0.0651 to 0.0557)	0.8787	0.0006 (–0.0013 to 0.0026)	0.5368	0.6917 (0.6764 to 0.7070)	0.9108
Model*+cumRC+RC variability	0.1352 (0.0779 to 0.1926)	<0.0001†	0.0029 (0.0014 to 0.0043)	<0.0001†	0.6940 (0.6787 to 0.7092)	0.2615
Change reference model						
Model*+cumRC	Reference		Reference		0.6930 (0.6778 to 0.7082)	-
Model*+cumRC+RC variability	0.1571 (0.1045 to 0.2098)	<0.0001†	0.0014 (0.0005 to 0.0024)	0.0036†	0.6940 (0.6787 to 0.7092)	0.4182

cumRC indicates cumulative remnant cholesterol; IDI, integrated discrimination improvement; NRI, net reclassification index; RC, remnant cholesterol; and SV, successive variation.

*The model comprised traditional cardiovascular risk factors, including age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate, and low-density lipoprotein cholesterol.

†Statistical significance ($P<0.05$).

drugs may directly impact the RC variability. To some extent, the variability of lipid levels may reflect the medication strength and the quality of the patient's self-care, both of which are associated with adverse health outcomes.[46] However, we found that there is still a significant correlation between RC variability and CAS, even after adjusting for the use of lipid-lowering agents or excluding individuals who used such drugs. Finally, higher RC variability may be related to poor control of disease status.[44] Patients with systemic conditions and generalized frailty may have higher variability of multiple biological parameters, not just RC.[12,44] High RC variability could be an epiphenomenon of these systemic conditions that increase the risk of CAS.

Another key finding was the joint associations of RC accumulation and variability with CAS. Our results indicate that the simultaneous existence of both high cumRC and high variability in RC pose the highest risk of CAS, and their combination had a superior predictive value beyond the use of cumRC alone. Notably, for individuals with normal or lower cumRC levels, greater RC level fluctuations still could promote disease progression. The above association still existed even when LDL-C target levels had been achieved. Our results provide novel insights into the pathogenesis of residual risk of atherosclerosis. CumRC and RC variability could yield important residual risk information. In clinical practice, clinicians more easily obtain repeated measurements of blood lipid parameter recordings and calculate the cumRC and RC variability, which may contribute to individual-level risk stratification for atherosclerosis and CVD and improve cardiovascular risk assessment. This also reminds us that not only cumRC but also RC variability could serve as the new therapeutic target. Despite the lack of intervention studies specifically targeting variability reduction, the implementation of lifestyle modifications, the use of lipid-lowering medications, and improved medication adherence have the potential to maintain low levels of RC over the long term while simultaneously reducing its fluctuation. However, further clinical trials are necessary to confirm the clinical benefits of these approaches.

There has been an increasing clinical interest in modulating RC. Several studies have shown that liraglutide, high-dose n–3 fatty acid supplementation, particularly icosapent ethyl, peroxisome proliferator-activated receptor alpha modulators, and RNA-based inhibitors for apolipoprotein C-III and angiopoietin-like 3 could serve as the novel candidates for markedly reducing RC levels.[47–50] However, the clinical benefits of RC-lowering therapy were different. A recent study suggested that using *icosapent ethyl* could reduce the concentrations of atherogenic remnant particle-cholesterol and concomitantly lessen the occurrence of certain cardiovascular events, and the effects have been demonstrated to be independent of statin treatment.[47] Another randomized controlled trial conducted in patients with type 2 diabetes found that the incidence of cardiovascular events

was not lower among those who received pemafibrate, although pemafibrate lowered RC levels.[51] Additionally, in a randomized crossover study in patients with combined hyperlipidemia, atorvastatin and simvastatin, in addition to reducing LDL-C levels, significantly reduced RC levels. This may be another potential mechanism to explain their cardiovascular benefits from statins.[52] The combination therapy with statin and other nonstatin lipid-lowering drugs also can be expected to be a new strategy for reducing RC. Previous studies have reported that the combination of ezetimibe or a proprotein convertase subtilisin/kexin type 9 inhibitor with statins could reduce RC to a greater extent than using them alone,[53] but whether this RC-lowering strategy can reduce residual CVD risk requires further clinical trials for confirmation. It is worth noting that there are no clinical trials directly targeting RC as a core intervention target, mostly focusing on additional clinical benefits brought by triglyceride intervention. Our study revealed that the association between RC and CAS risk was independent of triglyceride, but not vice versa. The cholesterol component carried on triglyceride-rich lipoproteins may be the main culprits for atherosclerosis, surpassing triglyceride. Some clinical trials of triglyceride-lowering interventions have not demonstrated a significant reduction in residual CVD risk,[51] indicating the urgent need to design and conduct studies prioritizing RC as a core intervention target.

Strengths and Limitations

Several advantages exist in our research. Our findings extend and refine evidence of the longitudinal associations between RC and CAS in the general population. Moreover, RC was measured repeatedly during long-term follow-up, and we considered both RC accumulation and variability to more accurately capture the longitudinal patterns of RC exposure over a period. Based on this, innovatively, we evaluated separate and joint associations of RC accumulation and variability with the risk of CAS for the first time. Finally, a range of sensitivity analyses were conducted to strengthen our conclusions.

This study also has some limitations. First, RC levels were not directly measured but obtained by calculation, which may deviate from the actual level and have overestimated values. However, the calculated and measured RC levels are closely correlated, and the calculated RC is widely used in many population studies.[54,55] Second, although we adjusted for several potential confounders, other unmeasured or residual confounders may still affect our findings. Moreover, for individuals without CAS, the carotid ultrasound information in the health examination database was only recorded as "no significant abnormalities" without continuous CIMT values, while specific continuous CIMT values were recorded only for individuals with CAS. However, we conducted a sensitivity analysis among those who developed CAS (with continuous CIMT values) to explore the associations between exposure variables and continuous CIMT and further confirmed our findings. Finally, our results in this single-cohort study need further validation in other populations.

CONCLUSIONS

In this prospective cohort of Chinese adults, we confirmed that higher cumRC as well as greater RC variability were each significantly associated with an elevated risk of CAS, regardless of traditional cardiovascular risk factors, including LDL-C and triglyceride. Their coexistence might further exacerbate the independent risk of CAS in the general population and provide incremental predictive value over traditional risk factors and single measured RC levels. Our study highlights the dual importance of not only aggressively lowering long-term cumulative exposure levels of RC but also avoiding large fluctuations simultaneously, even in people with optimal LDL-C level.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S13
Figures S1–S4

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Supplemental Material

Table S1. Baseline characteristics of the study population according to quartiles of cumulative remnant cholesterol.

Characteristics	Quartile 1 (n=1554)	Quartile 2 (n=1553)	Quartile 3 (n=1552)	Quartile 4 (n=1554)	*P* value
Age, years	43.00 [38.00, 49.00]	47.00 [41.00, 53.00]	48.00 [42.00, 53.00]	46.00 [41.00, 52.00]	<0.001
Male, n (%)	495 (31.9)	710 (45.7)	935 (60.2)	1183 (76.1)	<0.001
Hypertension, n (%)	282 (18.1)	465 (29.9)	655 (42.2)	866 (55.7)	<0.001
Diabetes, n (%)	77 (5.0)	111 (7.1)	192 (12.4)	284 (18.3)	<0.001
BMI, kg/m^2	22.46 [20.55, 24.34]	23.92 [21.97, 25.91]	25.14 [23.19, 27.32]	26.21 [24.41, 28.42]	<0.001
SBP, mmHg	110.00 [100.00, 120.00]	116.00 [109.00, 126.00]	120.00 [110.00, 130.00]	120.00 [113.00, 131.00]	<0.001
DBP, mmHg	70.00 [66.00, 80.00]	73.00 [69.00, 80.00]	80.00 [70.00, 84.00]	80.00 [72.00, 90.00]	<0.001
Fasting blood glucose, mmol/L	5.07 [4.79, 5.36]	5.19 [4.90, 5.50]	5.33 [5.02, 5.73]	5.41 [5.08, 5.90]	<0.001
Lipid-lowering medication use, n (%)	10 (0.6)	28 (1.8)	44 (2.8)	84 (5.4)	<0.001
Current smoker, n (%)	291 (18.7)	340 (21.9)	420 (27.1)	554 (35.6)	<0.001
Current drinker, n (%)	505 (32.5)	576 (37.1)	635 (40.9)	737 (47.4)	<0.001
Active physical activity, n (%)	647 (41.6)	634 (40.8)	724 (46.6)	674 (43.4)	0.005
SUA, μmol/L	250.00 [211.00, 301.40]	290.00 [237.10, 346.00]	325.95 [269.97, 384.00]	369.59 [312.12, 430.72]	< 0.001
eGFR, mL/min/1.73 m^2	108.62 [99.52, 115.30]	104.38 [94.67, 111.60]	102.67 [94.78, 109.63]	103.06 [94.01, 109.73]	< 0.001
Cumulative lipid level					
Cumulative RC, mg/dL×year	59.01 [54.48, 63.06]	74.97 [70.97, 79.85]	96.14 [90.29, 103.63]	140.53 [123.75, 174.35]	< 0.001
Cumulative TG, mg/dL×year	246.31 [209.98, 277.98]	365.03 [334.02, 400.47]	527.17 [476.67, 588.30]	910.81 [761.30, 1193.00]	< 0.001
Cumulative LDL-C, mg/dL×year	377.32 [322.47, 435.29]	443.28 [385.05, 500.65]	469.53 [409.18, 532.83]	461.79 [381.09, 541.92]	< 0.001
Cumulative HDL-C, mg/dL×year	236.60 [208.38, 265.98]	212.24 [186.73, 241.24]	192.14 [168.56, 218.82]	167.78 [150.39, 191.27]	< 0.001
Cumulative TC, mg/dL×year	674.04 [605.13, 741.50]	726.42 [661.86, 805.67]	756.19 [683.90, 836.99]	800.26 [720.53, 893.05]	< 0.001
RC variability					
SV, mg/dL	2.13 [1.28, 3.36]	3.62 [2.37, 5.36]	5.21 [3.11, 7.74]	9.27 [5.44, 17.39]	< 0.001
VIM	3.46 [2.07, 5.57]	4.33 [2.78, 6.03]	4.25 [2.57, 6.13]	4.35 [2.69, 6.86]	< 0.001

ARV, mg/dL	1.90 [1.14, 2.98]	3.20 [2.13, 4.82]	4.70 [2.76, 6.99]	8.38 [4.85, 15.69]	< 0.001
SD, mg/dL	1.57 [0.93, 2.43]	2.76 [1.76, 3.95]	3.91 [2.33, 5.58]	6.82 [4.21, 12.59]	< 0.001
CV	10.74 [6.41, 17.12]	14.75 [9.50, 20.44]	16.13 [9.77, 23.10]	19.60 [11.99, 31.50]	< 0.001
Outcomes					
Carotid atherosclerosis, n (%)	498 (32.0)	619 (39.9)	738 (47.6)	758 (48.8)	< 0.001
Carotid plaque, n (%)	198 (12.7)	307 (19.8)	381 (24.5)	441 (28.4)	< 0.001

Data are presented as the mean (SD), median [IQR] or number (%), as appropriate. Continuous variables were compared using one-way ANOVA test or Kruskal-Wallis test. Categorical variables were compared using χ^2 test or Fisher's exact test.

RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation; IQR, interquartile range; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S2. Baseline characteristics of the study population according to quartiles of remnant cholesterol variability (measured by SV).

Characteristics	Quartile 1 (n=1553)	Quartile 2 (n=1554)	Quartile 3 (n=1552)	Quartile 4 (n=1554)	*P* value
Age, years	45.00 [40.00, 52.00]	46.00 [41.00, 52.00]	46.00 [41.00, 52.00]	46.00 [41.00, 52.00]	0.002
Male, n (%)	661 (42.6)	714 (45.9)	873 (56.2)	1075 (69.2)	<0.001
Hypertension, n (%)	411 (26.5)	460 (29.6)	622 (40.1)	775 (49.9)	<0.001
Diabetes, n (%)	106 (6.8)	111 (7.1)	165 (10.6)	282 (18.1)	<0.001
BMI, kg/m^2	23.26 [21.21, 25.47]	23.83 [21.86, 26.21]	24.78 [22.72, 27.10]	25.68 [23.83, 27.74]	<0.001
SBP, mmHg	110.00 [103.00, 122.00]	116.00 [109.00, 124.00]	120.00 [110.00, 130.00]	120.00 [110.00, 130.00]	<0.001
DBP, mmHg	70.00 [66.00, 80.00]	74.00 [70.00, 80.00]	79.00 [70.00, 84.00]	80.00 [70.00, 88.00]	<0.001
Fasting blood glucose, mmol/L	5.14 [4.84, 5.45]	5.19 [4.88, 5.53]	5.27 [4.99, 5.62]	5.38 [5.04, 5.89]	<0.001
Lipid-lowering medication use, n (%)	20 (1.3)	33 (2.1)	41 (2.6)	72 (4.6)	<0.001
Current smoker, n (%)	311 (20)	369 (23.7)	409 (26.4)	516 (33.2)	<0.001
Current drinker, n (%)	576 (37.1)	559 (36.0)	625 (40.3)	693 (44.6)	<0.001
Active physical activity, n (%)	643 (41.4)	646 (41.6)	696 (44.8)	694 (44.7)	0.080
SUA, μmol/L	277.20 [224.20, 342.00]	290.18 [236.00, 352.53]	311.05 [255.81, 378.40]	348.05 [291.00, 413.22]	<0.001
eGFR, mL/min/1.73 m^2	105.71 [95.68, 113.08]	104.92 [95.85, 111.72]	104.29 [95.50, 111.18]	103.96 [95.38, 110.80]	0.001
Cumulative lipid level					
Cumulative RC, mg/dL×year	64.93 [57.47, 80.58]	74.76 [64.37, 92.33]	89.22 [74.16, 110.10]	123.9 [100.17, 165.90]	<0.001
Cumulative TG, mg/dL×year	292.38 [233.9, 406.67]	360.6 [286.18, 493.50]	467.36 [361.49, 632.38]	768.6 [553.75, 1135.85]	<0.001
Cumulative LDL-C, mg/dL×year	412.19 [349.10, 477.37]	430.48 [366.58, 501.03]	450.68 [388.53, 517.69]	451.92 [369.59, 523.07]	<0.001
Cumulative HDL-C, mg/dL×year	220.75 [191.37, 253.22]	210.70 [180.54, 244.23]	195.62 [171.17, 229.25]	176.68 [154.64, 204.12]	<0.001
Cumulative TC, mg/dL×year	708.25 [632.09, 780.55]	720.62 [652.58, 802.19]	745.94 [671.91, 826.94]	782.29 [700.52, 872.07]	<0.001
RC variability					
SV, mg/dL	1.46 [1.00, 1.87]	3.18 [2.76, 3.65]	5.51 [4.83, 6.31]	11.09 [8.87, 18.17]	<0.001
VIM	1.85 [1.19, 2.63]	3.68 [2.74, 4.78]	5.07 [3.83, 6.40]	6.85 [5.21, 8.94]	<0.001

ARV, mg/dL	1.30 [0.88, 1.66]	2.83 [2.48, 3.28]	4.97 [4.33, 5.73]	10.14 [7.99, 16.38]	<0.001
SD, mg/dL	1.10 [0.72, 1.43]	2.39 [2.02, 2.86]	4.09 [3.43, 4.79]	8.12 [6.20, 12.97]	<0.001
CV	6.10 [4.12, 8.43]	12.49 [9.78, 15.56]	18.21 [14.85, 22.36]	28.09 [21.99, 37.50]	<0.001
Outcomes					
Carotid atherosclerosis, n (%)	556 (35.8)	642 (41.3)	678 (43.7)	737 (47.4)	<0.001
Carotid plaque, n (%)	245 (15.8)	304 (19.6)	367 (23.6)	411 (26.4)	<0.001

Data are presented as the mean (SD), median [IQR] or number (%), as appropriate. Continuous variables were compared using one-way ANOVA test or Kruskal-Wallis test. Categorical variables were compared using χ^2 test or Fisher's exact test.

RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation; IQR, interquartile range; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S3. Rise or fall in RC with the risk of carotid atherosclerosis and carotid plaque,

	Carotid atherosclerosis		Carotid plaque	
	Cases, n (%)	**HR (95% CI)**	**Cases, n (%)**	**HR (95% CI)**
SV				
Stable	1198 (38.6)	Reference	549 (17.7)	Reference
Large fall	639 (47.2)	1.22 (1.09, 1.37)	338 (24.9)	1.22 (1.05, 1.40)
Large rise	776 (44.3)	1.12 (1.00, 1.25)	440 (25.1)	1.26 (1.10, 1.44)
VIM				
Stable	1277 (41.1)	Reference	651 (21.0)	Reference
Large fall	576 (44.6)	1.15 (1.03, 1.29)	278 (21.5)	1.07 (0.90, 1.26)
Large rise	760 (41.9)	1.12 (1.01, 1.25)	398 (21.9)	1.17 (1.01, 1.36)
ARV				
Stable	1197 (38.5)	Reference	554 (17.8)	Reference
Large fall	640 (47.0)	1.17 (1.06, 1.29)	334 (24.5)	1.19 (1.03, 1.37)
Large rise	776 (44.4)	1.10 (1.00, 1.21)	439 (25.1)	1.25 (1.09, 1.43)
SD				
Stable	1202 (38.7)	Reference	568 (18.3)	Reference
Large fall	633 (47.3)	1.21 (1.08, 1.36)	328 (24.5)	1.18 (1.02, 1.35)
Large rise	778 (44.0)	1.08 (0.96, 1.20)	431 (24.4)	1.20 (1.06, 1.37)
CV				
Stable	1253 (40.3)	Reference	612 (19,7)	Reference
Large fall	593 (45.5)	1.23 (1.10, 1.38)	302 (23.2)	1.19 (1.01, 1.41)
Large rise	767 (42.5)	1.11 (1.00, 1.24)	413 (22.9)	1.20 (1.03, 1.40)

Model was adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate, low-density lipoprotein cholesterol and cumRC.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

Table S4. Separate associations of cumRC and RC variability with the incidence of carotid atherosclerosis and carotid plaque after adjusting for cumulative triglyceride instead of low-density lipoprotein cholesterol.

	Carotid atherosclerosis		Carotid plaque	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
CumRC, mg/dL×year				
Quartile 1	Reference		Reference	
Quartile 2	1.18 (1.04, 1.33)	**0.009**	1.41 (1.18, 1.70)	**<0.001**
Quartile 3	1.33 (1.17, 1.51)	**<0.001**	1.61 (1.34, 1.94)	**<0.001**
Quartile 4	1.32 (1.13, 1.55)	**0.001**	1.88 (1.50, 2.35)	**<0.001**
Cumulative burden of RC				
=0	Reference		Reference	
>0	1.10 (0.99, 1.23)	0.081	1.17 (1.01, 1.35)	**0.037**
Exposure duration of high-RC*				
0 year	Reference		Reference	
2 years	1.14 (1.01, 1.28)	**0.030**	1.24 (1.05, 1.46)	**0.010**
4 years	1.13 (0.99, 1.30)	0.078	1.44 (1.20, 1.72)	**<0.001**
6 years	1.16 (0.99, 1.36)	0.071	1.41 (1.14, 1.74)	**0.001**
RC variability†				
SV (ref: Quartile 1)				
Quartile 2	1.20 (1.07, 1.35)	**0.002**	1.22 (1.03, 1.45)	**0.020**
Quartile 3	1.21 (1.08, 1.36)	**0.001**	1.38 (1.17, 1.63)	**<0.001**
Quartile 4	1.23 (1.09, 1.40)	**0.001**	1.42 (1.19, 1.70)	**<0.001**
VIM (ref: Quartile 1)				
Quartile 2	1.07 (0.94, 1.22)	0.292	1.18 (0.98, 1.42)	0.082
Quartile 3	1.17 (1.03, 1.33)	**0.017**	1.18 (0.98, 1.43)	0.084
Quartile 4	1.17 (1.03, 1.33)	**0.018**	1.24 (1.03, 1.50)	**0.024**
ARV (ref: Quartile 1)				
Quartile 2	1.19 (1.06, 1.34)	**0.002**	1.32 (1.11, 1.56)	**0.001**
Quartile 3	1.22 (1.09, 1.37)	**0.001**	1.42 (1.20, 1.67)	**<0.001**
Quartile 4	1.23 (1.08, 1.39)	**0.002**	1.46 (1.22, 1.75)	**<0.001**
SD (ref: Quartile 1)				
Quartile 2	1.20 (1.07, 1.35)	**0.001**	1.29 (1.09, 1.52)	**0.003**
Quartile 3	1.18 (1.06, 1.33)	**0.004**	1.30 (1.10, 1.53)	**0.002**
Quartile 4	1.23 (1.08, 1.40)	**0.001**	1.42 (1.19, 1.71)	**<0.001**
CV (ref: Quartile 1)				
Quartile 2	1.10 (0.96, 1.25)	0.170	1.15 (0.98, 1.35)	0.085
Quartile 3	1.21 (1.06, 1.37)	**0.005**	1.23 (1.05, 1.43)	**0.011**
Quartile 4	1.21 (1.06, 1.38)	**0.005**	1.18 (1.00, 1.39)	**0.045**

Model was adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate and cumulative triglyceride.

HR, hazard ratio; CI, confidence interval; cumRC, cumulative remnant cholesterol from visit 1 to visit 3 (2010-2015); SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV,

coefficient of variation; RC, remnant cholesterol.

* High-RC was defined as RC levels >28 mg/dL.

† Model were further adjusted for cumRC.

Table S5. Joint associations of cumRC and RC variability with the incidence of carotid atherosclerosis and carotid plaque after adjusting for cumulative triglyceride instead of low-density lipoprotein cholesterol.

	Carotid atherosclerosis		Carotid plaque	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Cutpoints: median of cumRC and SV				
Low cumRC and low SV	Reference		Reference	
Low cumRC and high SV	1.16 (1.02, 1.32)	**0.023**	1.30 (1.08, 1.57)	**0.006**
High cumRC and low SV	1.28 (1.12, 1.45)	**<0.001**	1.39 (1.16, 1.67)	**<0.001**
High cumRC and high SV	1.25 (1.12, 1.40)	**<0.001**	1.51 (1.29, 1.77)	**<0.001**
Cutpoints: median of cumRC and VIM				
Low cumRC and low VIM	Reference		Reference	
Low cumRC and high VIM	1.18 (1.03, 1.35)	**0.018**	1.15 (0.96, 1.37)	0.126
High cumRC and low VIM	1.27 (1.10, 1.47)	**0.001**	1.47 (1.23, 1.75)	**<0.001**
High cumRC and high VIM	1.38 (1.19, 1.59)	**<0.001**	1.41 (1.18, 1.68)	**<0.001**
Cutpoints: median of cumRC and ARV				
Low cumRC and low ARV	Reference		Reference	
Low cumRC and high ARV	1.11 (0.98, 1.27)	0.109	1.20 (0.99, 1.45)	0.062
High cumRC and low ARV	1.22 (1.07, 1.39)	**0.003**	1.32 (1.10, 1.59)	**0.003**
High cumRC and high ARV	1.26 (1.12, 1.41)	**<0.001**	1.49 (1.27, 1.74)	**<0.001**
Cutpoints: median of cumRC and SD				
Low cumRC and low SD	Reference		Reference	
Low cumRC and high SD	1.14 (1.00, 1.30)	**0.046**	1.18 (0.97, 1.43)	0.091
High cumRC and low SD	1.28 (1.13, 1.46)	**<0.001**	1.39 (1.16, 1.66)	**<0.001**
High cumRC and high SD	1.24 (1.11, 1.39)	**<0.001**	1.44 (1.23, 1.68)	**<0.001**
Cutpoints: median of cumRC and CV				
Low cumRC and low CV	Reference		Reference	
Low cumRC and high CV	1.15 (1.00, 1.32)	**0.044**	1.13 (0.95, 1.35)	0.166
High cumRC and low CV	1.22 (1.05, 1.41)	**0.007**	1.37 (1.15, 1.63)	**<0.001**
High cumRC and high CV	1.37 (1.19, 1.57)	**<0.001**	1.47 (1.24, 1.74)	**<0.001**

Model was adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate and cumulative triglyceride.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

Table S6. Associations between cumulative triglyceride levels and the incidence of carotid atherosclerosis and carotid plaque.

	HR (95%CI)					
	Model	***P* value**	**Model+LDL-C**	***P* value**	**Model+RC**	***P* value**
Carotid atherosclerosis						
Cumulative TG, mg/dL×year						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.12 (0.99, 1.26)	**0.062**	1.03 (0.91, 1.16)	0.682	0.92 (0.72, 1.18)	0.500
Quartile 3	1.34 (1.19, 1.52)	**<0.001**	1.20 (1.06, 1.36)	**0.004**	1.05 (0.77, 1.44)	0.749
Quartile 4	1.26 (1.10, 1.43)	**0.001**	1.18 (1.03, 1.34)	**0.015**	0.84 (0.58, 1.22)	0.366
Carotid plaque						
Cumulative TG, mg/dL×year						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.44 (1.20, 1.72)	**<0.001**	1.30 (1.08, 1.55)	**0.005**	1.20 (0.83, 1.72)	0.341
Quartile 3	1.58 (1.32, 1.89)	**<0.001**	1.37 (1.14, 1.64)	**0.001**	1.03 (0.65, 1.62)	0.900
Quartile 4	1.67 (1.38, 2.03)	**<0.001**	1.53 (1.26, 1.85)	**<0.001**	0.80 (0.47, 1.35)	0.402

Model: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid and estimated glomerular filtration rate.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; cumulative TG, cumulative triglyceride from visit 1 to visit 3 (2010-2015).

Table S7. Separate associations of cumRC and RC variability with continuous carotid intima-media thickness among 2613 participants.

	β (95%CI)			
	Model1	***P* value**	**Model2**	***P* value**
CumRC (ref: Quartile 1)				
Quartile 2	0.06 (0.01, 0.12)	**0.024**	0.06 (0.00, 0.12)	0.059
Quartile 3	0.07 (0.01, 0.12)	**0.016**	0.07 (0.01, 0.13)	**0.021**
Quartile 4	0.09 (0.04, 0.15)	**0.001**	0.05 (0.00, 0.09)	**0.049**
Cumulative burden of RC (ref: =0)				
>0	0.03 (-0.01, 0.07)	0.099	0.02 (-0.02, 0.06)	0.235
Exposure duration of high-RC* (ref: 0 year)				
2 years	0.04 (-0.01, 0.09)	0.121	0.03 (-0.02, 0.09)	0.196
4 years	0.04 (-0.02, 0.10)	0.220	0.03 (-0.03, 0.09)	0.338
6 years	0.07 (0.02, 0.13)	**0.006**	0.06 (0.01, 0.12)	**0.023**
RC variability†				
SV (ref: Quartile 1)				
Quartile 2	0.02 (-0.04, 0.07)	0.540	0.01 (-0.04, 0.07)	0.623
Quartile 3	0.06 (0.01, 0.12)	**0.021**	0.05 (0.00, 0.11)	**0.045**
Quartile 4	0.06 (0.01, 0.11)	**0.024**	0.05 (0.00, 0.11)	**0.043**
VIM (ref: Quartile 1)				
Quartile 2	0.01 (-0.05, 0.07)	0.747	0.01 (-0.05, 0.07)	0.753
Quartile 3	0.02 (-0.05, 0.08)	0.618	0.02 (-0.04, 0.08)	0.585
Quartile 4	0.02 (-0.04, 0.09)	0.432	0.03 (-0.03, 0.09)	0.388
ARV (ref: Quartile 1)				
Quartile 2	0.03 (-0.02, 0.09)	0.245	0.03 (-0.02, 0.08)	0.293
Quartile 3	0.04 (-0.01, 0.09)	0.141	0.03 (-0.02, 0.09)	0.225
Quartile 4	0.07 (0.01, 0.12)	**0.012**	0.06 (0.01, 0.11)	**0.024**
SD (ref: Quartile 1)				
Quartile 2	0.04 (-0.01, 0.09)	0.158	0.03 (-0.02, 0.09)	0.224
Quartile 3	0.04 (-0.01, 0.09)	0.123	0.03 (-0.02, 0.09)	0.224
Quartile 4	0.06 (0.01, 0.11)	**0.032**	0.05 (0.00, 0.10)	0.062
CV (ref: Quartile 1)				
Quartile 2	-0.01 (-0.07, 0.05)	0.809	-0.01 (-0.07, 0.05)	0.756
Quartile 3	0.04 (-0.03, 0.10)	0.254	0.03 (-0.03, 0.09)	0.284
Quartile 4	0.03 (-0.03, 0.09)	0.297	0.03 (-0.03, 0.09)	0.324

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate and the follow-up duration.
Model 2: further adjusted for low-density lipoprotein cholesterol.

β, unstandardized coefficients; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol from visit 1 to visit 3 (2010-2015); SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

* High-RC was defined as RC levels >28 mg/dL.

† Model 1 and Model 2 were further adjusted for cumRC.

Table S8. Joint associations of cumRC and RC variability with continuous carotid intima-media thickness among 2613 participants.

	β (95% CI)			
	Model1	***P* value**	**Model2**	***P* value**
Cutpoints: median of cumRC and SV				
Low cumRC and low SV	Reference		Reference	
Low cumRC and high SV	0.09 (0.03, 0.15)	**0.004**	0.08 (0.02, 0.15)	**0.006**
High cumRC and low SV	0.08 (0.02, 0.14)	**0.007**	0.07 (0.01, 0.12)	**0.024**
High cumRC and high SV	0.07 (0.02, 0.11)	**0.003**	0.06 (0.01, 0.10)	**0.013**
Cutpoints: median of cumRC and VIM				
Low cumRC and low VIM	Reference		Reference	
Low cumRC and high VIM	0.04 (-0.03, 0.10)	0.275	0.03 (-0.03, 0.10)	0.295
High cumRC and low VIM	0.08 (0.02, 0.15)	**0.012**	0.07 (0.00, 0.13)	**0.039**
High cumRC and high VIM	0.07 (0.01, 0.13)	**0.030**	0.06 (0.00, 0.12)	0.060
Cutpoints: median of cumRC and ARV				
Low cumRC and low ARV	Reference		Reference	
Low cumRC and high ARV	0.06 (0.00, 0.13)	**0.041**	0.06 (0.00, 0.12)	0.059
High cumRC and low ARV	0.08 (0.02, 0.14)	**0.006**	0.07 (0.01, 0.13)	**0.021**
High cumRC and high ARV	0.06 (0.01, 0.10)	**0.013**	0.05 (0.00, 0.09)	**0.049**
Cutpoints: median of cumRC and SD				
Low cumRC and low SD	Reference		Reference	
Low cumRC and high SD	0.06 (0.00, 0.12)	0.056	0.05 (-0.01, 0.12)	0.082
High cumRC and low SD	0.09 (0.03, 0.15)	**0.002**	0.08 (0.02, 0.13)	**0.010**
High cumRC and high SD	0.05 (0.01, 0.10)	**0.025**	0.04 (-0.01, 0.09)	0.081
Cutpoints: median of cumRC and CV				
Low cumRC and low CV	Reference		Reference	
Low cumRC and high CV	0.05 (-0.02, 0.11)	0.166	0.04 (-0.02, 0.11)	0.181
High cumRC and low CV	0.07 (0.01, 0.14)	**0.026**	0.06 (0.00, 0.12)	0.071
High cumRC and high CV	0.08 (0.02, 0.13)	**0.008**	0.07 (0.01, 0.13)	**0.023**

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid, estimated glomerular filtration rate and the follow-up duration.

Model 2: further adjusted for low-density lipoprotein cholesterol.

β, unstandardized coefficients; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

Table S9. Separate associations of cumRC and RC variability with the incidence of carotid atherosclerosis after excluding participants taking lipid-lowering agents.

	HR (95%CI)			
	Model1	***P* value**	**Model2**	***P* value**
CumRC (ref: Quartile 1)				
Quartile 2	1.18 (1.04, 1.33)	**0.009**	1.06 (0.94, 1.20)	0.359
Quartile 3	1.33 (1.18, 1.51)	**<0.001**	1.16 (1.02, 1.31)	**0.027**
Quartile 4	1.33 (1.17, 1.52)	**<0.001**	1.17 (1.02, 1.34)	**0.026**
Cumulative burden of RC (ref: =0)				
>0	1.12 (1.03, 1.23)	**0.012**	1.06 (0.96, 1.16)	0.238
Exposure duration of high-RC* (ref: 0 year)				
2 years	1.12 (0.99, 1.26)	0.064	1.07 (0.95, 1.20)	0.294
4 years	1.15 (1.01, 1.31)	**0.042**	1.06 (0.93, 1.21)	0.403
6 years	1.19 (1.05, 1.34)	**0.006**	1.12 (0.99, 1.27)	0.077
RC variability †				
SV (ref: Quartile 1)				
Quartile 2	1.22 (1.09, 1.37)	**0.001**	1.19 (1.06, 1.34)	**0.003**
Quartile 3	1.22 (1.09, 1.37)	**0.001**	1.15 (1.03, 1.30)	**0.016**
Quartile 4	1.23 (1.09, 1.40)	**0.001**	1.18 (1.04, 1.34)	**0.013**
VIM (ref: Quartile 1)				
Quartile 2	1.07 (0.94, 1.22)	0.306	1.07 (0.93, 1.22)	0.342
Quartile 3	1.18 (1.03, 1.34)	**0.015**	1.17 (1.03, 1.33)	**0.018**
Quartile 4	1.19 (1.04, 1.36)	**0.010**	1.21 (1.06, 1.38)	**0.005**
ARV (ref: Quartile 1)				
Quartile 2	1.20 (1.07, 1.35)	**0.002**	1.18 (1.05, 1.32)	**0.006**
Quartile 3	1.22 (1.09, 1.38)	**0.001**	1.15 (1.03, 1.30)	**0.018**
Quartile 4	1.22 (1.07, 1.39)	**0.002**	1.16 (1.02, 1.32)	**0.020**
SD (ref: Quartile 1)				
Quartile 2	1.21 (1.08, 1.36)	**0.001**	1.18 (1.05, 1.32)	**0.006**
Quartile 3	1.19 (1.06, 1.33)	**0.004**	1.11 (0.99, 1.25)	0.079
Quartile 4	1.24 (1.09, 1.41)	**0.001**	1.17 (1.03, 1.33)	**0.016**
CV (ref: Quartile 1)				
Quartile 2	1.09 (0.96, 1.25)	0.192	1.08 (0.95, 1.23)	0.259
Quartile 3	1.21 (1.06, 1.38)	**0.004**	1.19 (1.04, 1.35)	**0.012**
Quartile 4	1.22 (1.06, 1.40)	**0.004**	1.21 (1.06, 1.39)	**0.005**

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol from visit 1 to visit 3 (2010-2015); SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

* High-RC was defined as RC levels >28 mg/dL.

† Model 1 and Model 2 were further adjusted for cumRC.

Table S10. Joint associations of cumRC and RC variability with the incidence of carotid atherosclerosis after excluding participants taking lipid-lowering agents.

	HR (95% CI)			
	Model1	***P* value**	**Model2**	***P* value**
Cutpoints: median of cumRC and SV				
Low cumRC and low SV	Reference		Reference	
Low cumRC and high SV	1.18 (1.03, 1.34)	**0.014**	1.14 (1.00, 1.30)	**0.050**
High cumRC and low SV	1.29 (1.14, 1.47)	**<0.001**	1.17 (1.03, 1.33)	**0.018**
High cumRC and high SV	1.26 (1.14, 1.40)	**<0.001**	1.17 (1.06, 1.30)	**0.003**
Cutpoints: median of cumRC and VIM				
Low cumRC and low VIM	Reference		Reference	
Low cumRC and high VIM	1.18 (1.03, 1.35)	**0.019**	1.17 (1.02, 1.34)	**0.027**
High cumRC and low VIM	1.24 (1.08, 1.43)	**0.003**	1.12 (0.97, 1.30)	0.116
High cumRC and high VIM	1.37 (1.20, 1.57)	**<0.001**	1.28 (1.12, 1.47)	**<0.001**
Cutpoints: median of cumRC and ARV				
Low cumRC and low ARV	Reference		Reference	
Low cumRC and high ARV	1.12 (0.98, 1.28)	0.089	1.08 (0.94, 1.23)	0.279
High cumRC and low ARV	1.23 (1.08, 1.40)	**0.002**	1.11 (0.97, 1.26)	0.122
High cumRC and high ARV	1.26 (1.14, 1.40)	**<0.001**	1.17 (1.05, 1.30)	**0.003**
Cutpoints: median of cumRC and SD				
Low cumRC and low SD	Reference		Reference	
Low cumRC and high SD	1.15 (1.01, 1.31)	**0.040**	1.10 (0.97, 1.26)	0.145
High cumRC and low SD	1.28 (1.13, 1.46)	**<0.001**	1.16 (1.01, 1.32)	**0.030**
High cumRC and high SD	1.25 (1.13, 1.39)	**<0.001**	1.16 (1.05, 1.29)	**0.005**
Cutpoints: median of cumRC and CV				
Low cumRC and low CV	Reference		Reference	
Low cumRC and high CV	1.15 (1.00, 1.33)	**0.044**	1.13 (0.98, 1.30)	0.084
High cumRC and low CV	1.19 (1.03, 1.37)	**0.018**	1.07 (0.92, 1.24)	0.372
High cumRC and high CV	1.35 (1.19, 1.53)	**<0.001**	1.25 (1.10, 1.43)	**0.001**

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

Table S11. Separate associations of cumRC and RC variability with the incidence of carotid atherosclerosis after excluding participants who developed carotid atherosclerosis within the first 1 year of follow-up.

	HR (95%CI)			
	Model1	***P* value**	**Model2**	***P* value**
CumRC (ref: Quartile 1)				
Quartile 2	1.15 (1.01, 1.30)	**0.040**	1.02 (0.90, 1.17)	0.741
Quartile 3	1.34 (1.17, 1.52)	**<0.001**	1.17 (1.02, 1.34)	**0.024**
Quartile 4	1.35 (1.17, 1.55)	**<0.001**	1.21 (1.05, 1.40)	**0.008**
Cumulative burden of RC (ref: =0)				
>0	1.14 (1.04, 1.26)	**0.007**	1.06 (0.97, 1.17)	0.198
Exposure duration of high-RC* (ref: 0 year)				
2 years	1.15 (1.02, 1.31)	**0.023**	1.10 (0.97, 1.24)	0.150
4 years	1.16 (1.01, 1.33)	**0.039**	1.10 (0.95, 1.26)	0.190
6 years	1.23 (1.09, 1.40)	**0.001**	1.19 (1.05, 1.35)	**0.008**
RC variability†				
SV (ref: Quartile 1)				
Quartile 2	1.18 (1.05, 1.33)	**0.005**	1.17 (1.04, 1.31)	**0.009**
Quartile 3	1.19 (1.06, 1.34)	**0.004**	1.15 (1.02, 1.29)	**0.020**
Quartile 4	1.19 (1.05, 1.35)	**0.008**	1.17 (1.03, 1.33)	**0.015**
VIM (ref: Quartile 1)				
Quartile 2	1.10 (0.98, 1.23)	0.105	1.11 (0.99, 1.24)	0.079
Quartile 3	1.13 (1.01, 1.26)	**0.037**	1.14 (1.02, 1.27)	**0.023**
Quartile 4	1.06 (0.94, 1.19)	0.332	1.08 (0.96, 1.21)	0.182
ARV (ref: Quartile 1)				
Quartile 2	1.18 (1.05, 1.32)	**0.006**	1.17 (1.04, 1.31)	**0.010**
Quartile 3	1.20 (1.06, 1.35)	**0.003**	1.16 (1.03, 1.31)	**0.012**
Quartile 4	1.20 (1.05, 1.36)	**0.006**	1.18 (1.04, 1.34)	**0.012**
SD (ref: Quartile 1)				
Quartile 2	1.20 (1.06, 1.34)	**0.003**	1.19 (1.06, 1.34)	**0.004**
Quartile 3	1.16 (1.03, 1.31)	**0.011**	1.13 (1.01, 1.27)	**0.038**
Quartile 4	1.20 (1.05, 1.37)	**0.006**	1.18 (1.04, 1.35)	**0.012**
CV (ref: Quartile 1)				
Quartile 2	1.13 (1.00, 1.26)	**0.042**	1.13 (1.01, 1.27)	**0.038**
Quartile 3	1.19 (1.06, 1.33)	**0.003**	1.19 (1.06, 1.33)	**0.004**
Quartile 4	1.09 (0.97, 1.23)	0.156	1.11 (0.98, 1.25)	0.100

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol from visit 1 to visit 3 (2010-2015); SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

* High-RC was defined as RC levels >28 mg/dL.

† Model 1 and Model 2 were further adjusted for cumRC.

Table S12. Joint associations of cumRC and RC variability with the incidence of carotid atherosclerosis after excluding participants who developed carotid atherosclerosis within the first 1 year of follow-up.

	HR (95% CI)			
	Model1	***P* value**	**Model2**	***P* value**
Cutpoints: median of cumRC and SV				
Low cumRC and low SV	Reference		Reference	
Low cumRC and high SV	1.25 (1.03, 1.52)	**0.024**	1.22 (1.01, 1.49)	**0.044**
High cumRC and low SV	1.35 (1.12, 1.63)	**0.002**	1.24 (1.02, 1.49)	**0.028**
High cumRC and high SV	1.47 (1.26, 1.71)	**<0.001**	1.38 (1.19, 1.60)	**<0.001**
Cutpoints: median of cumRC and VIM				
Low cumRC and low VIM	Reference		Reference	
Low cumRC and high VIM	1.11 (0.98, 1.25)	0.097	1.11 (0.98, 1.25)	0.101
High cumRC and low VIM	1.29 (1.14, 1.46)	**<0.001**	1.22 (1.08, 1.38)	**0.002**
High cumRC and high VIM	1.28 (1.14, 1.44)	**<0.001**	1.24 (1.10, 1.40)	**<0.001**
Cutpoints: median of cumRC and ARV				
Low cumRC and low ARV	Reference		Reference	
Low cumRC and high ARV	1.09 (0.95, 1.24)	0.229	1.06 (0.93, 1.21)	0.396
High cumRC and low ARV	1.23 (1.08, 1.41)	**0.001**	1.15 (1.01, 1.32)	**0.032**
High cumRC and high ARV	1.26 (1.14, 1.40)	**<0.001**	1.21 (1.09, 1.34)	**<0.001**
Cutpoints: median of cumRC and SD				
Low cumRC and low SD	Reference		Reference	
Low cumRC and high SD	1.12 (0.97, 1.28)	0.114	1.09 (0.95, 1.25)	0.216
High cumRC and low SD	1.30 (1.14, 1.48)	**<0.001**	1.22 (1.07, 1.39)	**0.003**
High cumRC and high SD	1.25 (1.13, 1.39)	**<0.001**	1.19 (1.07, 1.33)	**0.001**
Cutpoints: median of cumRC and CV				
Low cumRC and low CV	Reference		Reference	
Low cumRC and high CV	1.09 (0.97, 1.24)	0.152	1.09 (0.96, 1.23)	0.175
High cumRC and low CV	1.24 (1.10, 1.40)	**0.001**	1.17 (1.03, 1.32)	**0.015**
High cumRC and high CV	1.29 (1.16, 1.45)	**<0.001**	1.25 (1.11, 1.39)	**<0.001**

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

Table S13. Separate and joint Associations of cumRC and RC variability with the incidence of vulnerable carotid plaque.

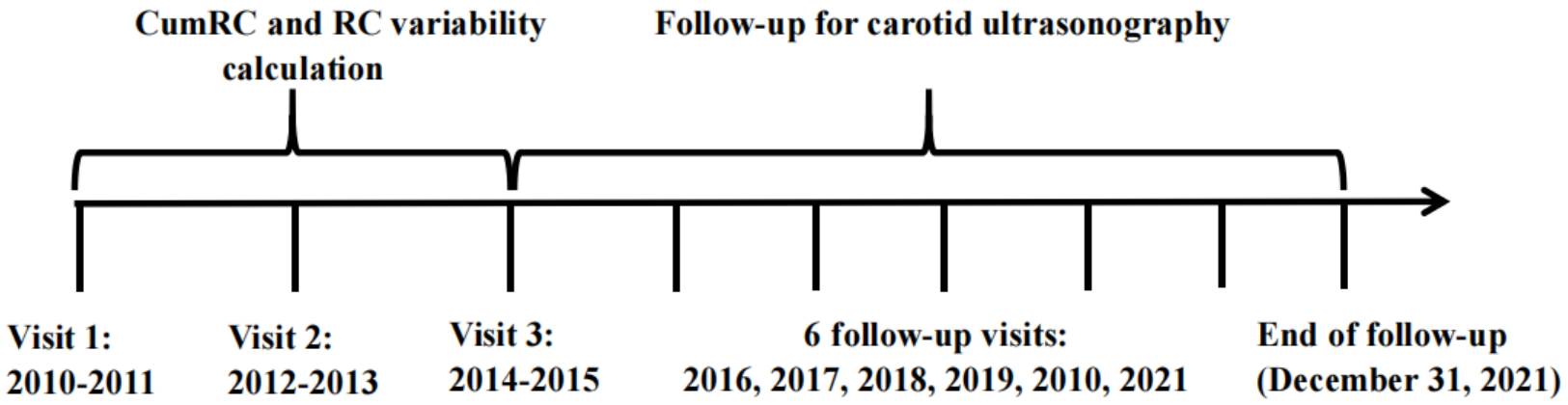
	HR (95% CI)			
	Model1	***P* value**	**Model2**	***P* value**
CumRC (ref: Quartile 1)				
Quartile 2	1.36 (0.98, 1.89)	0.062	1.16 (0.84, 1.62)	0.370
Quartile 3	1.46 (1.06, 2.02)	**0.022**	1.18 (0.84, 1.64)	0.341
Quartile 4	1.86 (1.33, 2.61)	**<0.001**	1.50 (1.06, 2.12)	**0.021**
RC variability*				
SV (ref: Quartile 1)				
Quartile 2	1.25 (0.93, 1.66)	0.137	1.22 (0.91, 1.63)	0.186
Quartile 3	1.42 (1.08, 1.88)	**0.013**	1.34 (1.01, 1.78)	**0.039**
Quartile 4	1.42 (1.05, 1.92)	**0.022**	1.37 (1.01, 1.85)	**0.041**
VIM (ref: Quartile 1)				
Quartile 2	1.09 (0.85, 1.41)	0.495	1.08 (0.84, 1.40)	0.534
Quartile 3	1.03 (0.80, 1.34)	0.798	1.03 (0.80, 1.33)	0.821
Quartile 4	0.93 (0.71, 1.21)	0.571	0.94 (0.72, 1.23)	0.659
ARV (ref: Quartile 1)				
Quartile 2	1.33 (1.00, 1.77)	**0.049**	1.28 (0.96, 1.71)	0.086
Quartile 3	1.37 (1.03, 1.81)	**0.029**	1.30 (0.98, 1.73)	0.066
Quartile 4	1.40 (1.04, 1.89)	**0.026**	1.36 (1.01, 1.83)	**0.045**
SD (ref: Quartile 1)				
Quartile 2	1.30 (0.97, 1.72)	0.075	1.25 (0.94, 1.67)	0.121
Quartile 3	1.36 (1.02, 1.80)	**0.033**	1.28 (0.96, 1.69)	0.090
Quartile 4	1.38 (1.02, 1.87)	**0.040**	1.34 (0.98, 1.81)	0.063
CV (ref: Quartile 1)				
Quartile 2	1.04 (0.79, 1.35)	0.792	1.01 (0.78, 1.32)	0.913
Quartile 3	1.12 (0.87, 1.45)	0.384	1.11 (0.86, 1.44)	0.435
Quartile 4	1.03 (0.78, 1.36)	0.823	1.05 (0.80, 1.38)	0.742
Combination of cumRC and variability (measured by SV)				
Cutpoints: median of cumRC and SV				
Low cumRC and low SV	Reference		Reference	
Low cumRC and high SV	1.39 (1.00, 1.93)	**0.048**	1.35 (0.97, 1.88)	0.072
High cumRC and low SV	1.42 (1.05, 1.92)	**0.023**	1.34 (0.99, 1.81)	0.062
High cumRC and high SV	1.53 (1.20, 1.95)	**0.001**	1.44 (1.13, 1.85)	**0.003**

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

HR, hazard ratio; CI, confidence interval; RC, remnant cholesterol; cumRC, cumulative remnant cholesterol; SV, successive variation; VIM, variability independent of the mean; ARV, average real variability; SD, standard deviation; CV, coefficient of variation.

* Model 1 and Model 2 were further adjusted for cumRC.

Figure S1. The timeline of the study.



RC, remnant cholesterol; cumRC, cumulative remnant cholesterol.

Figure S2. Study flowchart of participant selection.

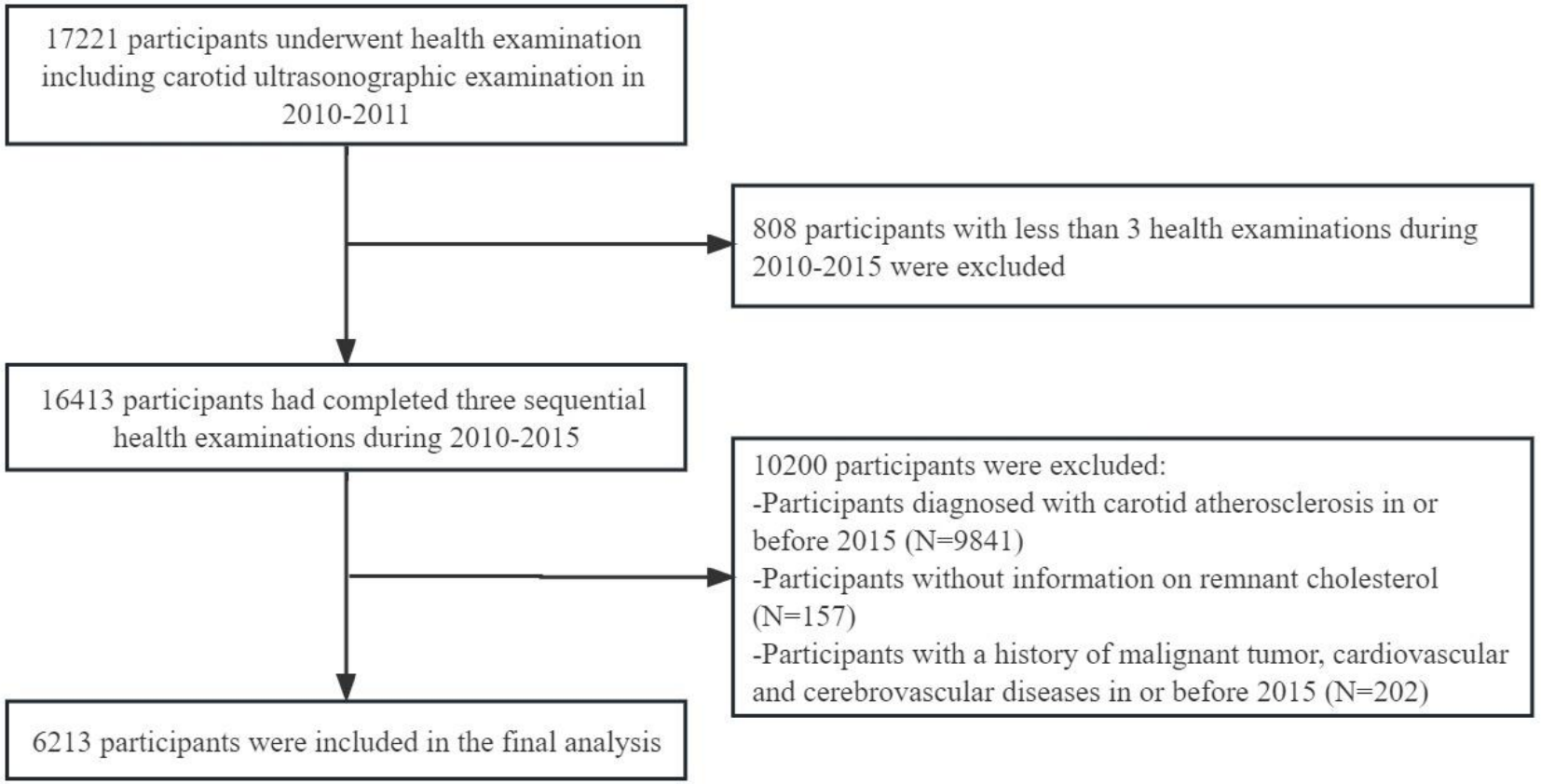
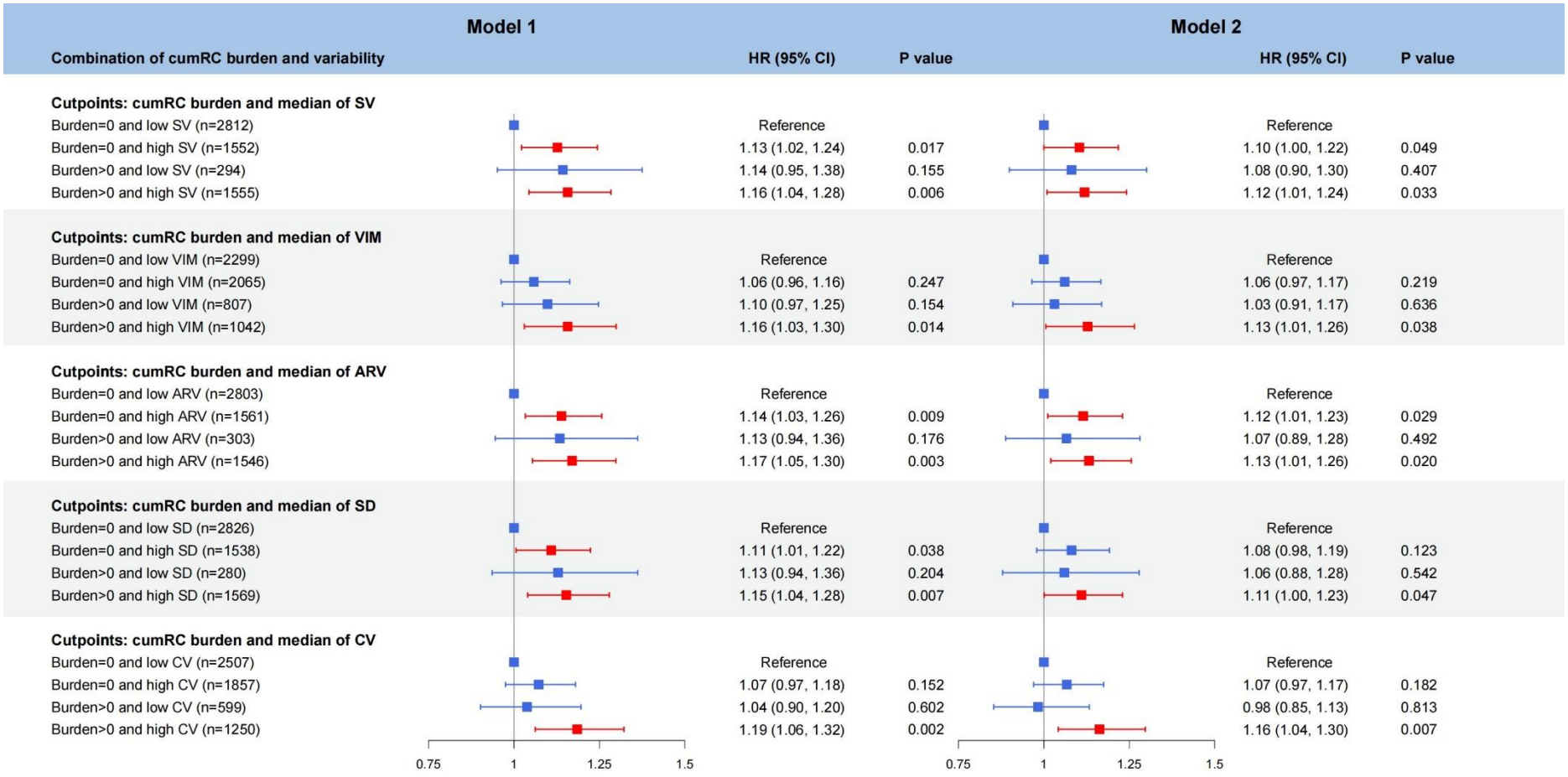


Figure S3. Joint associations of cumRC and RC variability with the incidence of carotid atherosclerosis after participants were divided into 4 combined groups according to cumRC burden and the median of RC variability.



ARV, average real variability; CI, confidence interval; CV, coefficient of variation; cumRC, cumulative remnant cholesterol; HR, hazard ratio; RC, remnant cholesterol; SD,

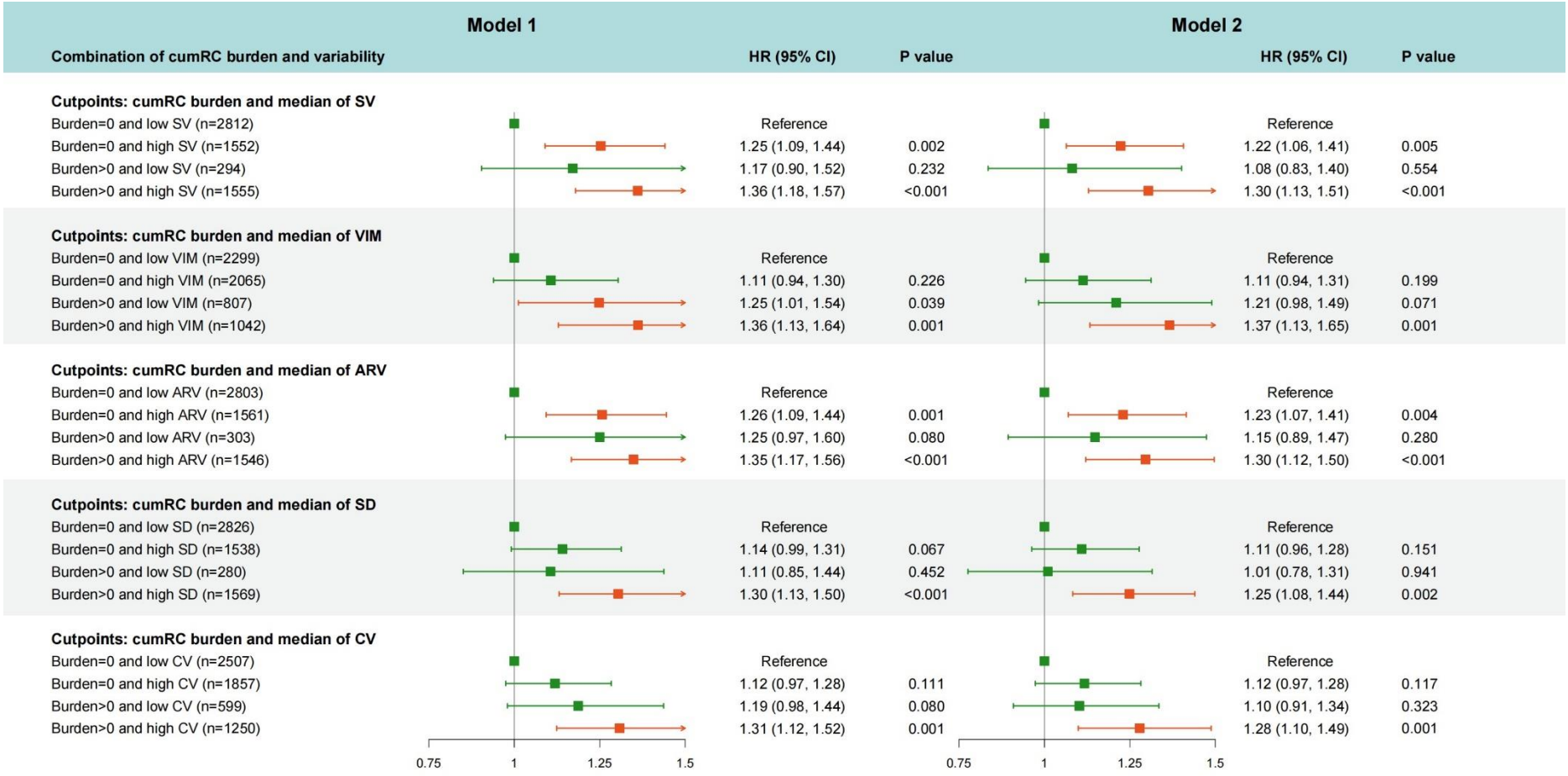
standard deviation; SV, successive variation; VIM, variability independent of the mean.

Graphs show HR and 95% CIs for the incidence of carotid atherosclerosis in model 1 and model 2.

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

Red means HR value is statistically significant, blue means HR value is not statistically significant.

Figure S4. Joint associations of cumRC and RC variability with the incidence of carotid plaque after participants were divided into 4 combined groups according to cumRC burden the median of RC variability



ARV, average real variability; CI, confidence interval; CV, coefficient of variation; cumRC, cumulative remnant cholesterol; HR, hazard ratio; RC, remnant cholesterol; SD,

standard deviation; SV, successive variation; VIM, variability independent of the mean.

Graphs show HR and 95% CIs for the incidence of carotid plaque in model 1 and model 2.

Model 1: adjusted for age, sex, smoking status, drinking status, physical activity, body mass index, hypertension, type 2 diabetes, use of lipid-lowering medications, serum uric acid and estimated glomerular filtration rate. Model 2: further adjusted for low-density lipoprotein cholesterol.

Orange means HR value is statistically significant, green means HR value is not statistically significant.