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Elevated serum uric acid was associated with pre-inflammatory state and impacted the role of HDL-C on carotid atherosclerosis

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KEYWORDS
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Abstract *Background and aims:* Uric acid (UA) and high-density lipoprotein cholesterol (HDL-C) are positively and negatively associated with atherosclerosis, respectively. UA and HDL-C are involved in the balance of proinflammatory and anti-inflammatory processes in atherosclerosis. However, it is still unclear whether UA affects the effect of HDL-C on atherosclerosis.
Methods and results: In this retrospective study, we enrolled 1437 patients with multiple risk factors for atherosclerosis. Patients were categorized into two groups according to their baseline UA level. Multivariate logistic regression analysis and restricted cubic spline curves were used to assess the relationship between HDL-C and carotid atherosclerosis (abnormal carotid intima−media thickness [cIMT] and carotid artery plaque) at different UA levels. Compared to patients with normouricemia, patients with hyperuricemia were older and had a more extensive history of disease and unhealthy behavior. In the normouricemia group, multivariate-adjusted odds ratios (95% CIs) for HDL-C were 0.55 (0.33−0.92) for abnormal mean cIMT, 0.59 (0.35−1.00) for abnormal maximum cIMT, and 0.53 (0.29−0.94) for the occurrence of carotid artery plaque, while the correlation between each of these three indicators with HDL-C were not significant in those with hyperuricemia. Spline regression models yielded similar results. The effect of UA on the association between HDL-C and carotid atherosclerosis remained in the subset of patients with optimal low-density lipoprotein cholesterol.
Conclusion: Elevated UA marks a pre-inflammatory state and impacts the role of HDL-C on carotid atherosclerosis.

Abbreviations: UA, Uric acid; HDL-C, High-density lipoprotein cholesterol; cIMT, Carotid intima−media thickness; ASCVD, Atherosclerosis cardiovascular disease; CRP, C-reactive protein; OR, Odds ratio; 95% CI, 95% confidence interval; WBC, White blood cell; TG, Triglyceride; TC, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol.

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1. Introduction

Atherosclerosis is the most common cause of cardiovascular disease, with the highest morbidity and mortality. Serum uric acid (UA), the final product of purine metabolism, has a dual role of oxidation and anti-oxidation. According to emerging evidence from epidemiological and genetic studies, elevated UA plays an important role in the development and progression of atherosclerotic cardiovascular disease (ASCVD) [1,2]. Hyperuricemia is associated with inflammatory response and oxidative stress and leads to endothelial dysfunction, which promotes the development of atherosclerosis and plaque [3]. Several studies have indicated that hyperuricemia is not only associated with risk factors for ASCVD, but is itself a risk factor for ASCVD [4,5]. Thus, it may be hypothesized that UA interacts with other risk factors in the process of atherosclerosis.

High-density lipoprotein cholesterol (HDL-C) is a plasma lipoprotein with good anti-inflammatory and antioxidant properties. Endothelial protection and reverse cholesterol transport form the core function of HDL-C against atherosclerosis [6]. As one of the manifestations of dyslipidemia, low HDL-C level increases the oxidative status of the body [7]. HDL-C and UA have opposite effects on atherosclerosis, and both the high UA and the low HDL-C levels are associated with increased ASCVD risk and mortality [8,9]. Onat et al. proposed that elevated serum UA levels were accompanied by a proinflammatory state and HDL dysfunction [10]. Using the Mendelian randomization method, Biradar et al. showed that hyperuricemia could increase the risk of metabolic syndrome by lowering HDL-C level [11]. However, in a Japanese cohort followed up for 5 years, Kuwabara et al. found that the elevated level of UA was not an independent risk factor for low HDL-C [12]. The interaction between UA and HDL-C in serum and biological function is complex, and their contribution to the atherosclerosis process is still unknown.

Carotid intima–media thickness (cIMT) and carotid artery plaque, noninvasively measured by carotid artery ultrasonography, are surrogate markers of the presence and progression of atherosclerosis [13,14]. Previous studies have reported that the influence of UA and HDL-C on atherosclerosis can be reflected by cIMT and carotid artery plaque [15–20]. Early detection and treatment of atherosclerosis in subclinical setting can help prevent ASCVD events and significantly reduce the risk of death [21]. For effectively prevention of ASCVD, it is increasingly important to weigh the effects between risk factors. In view of the conflict between the antioxidant and prooxidant properties of UA, as well as the potential metabolic relationship between UA and HDL-C, our study aimed to clarify whether the effect of HDL-C on carotid atherosclerosis could be affected by different level of UA. In addition, we assessed the degree of inflammation in different situations and preliminarily explored possible mechanisms.

2. Methods

2.1. Study population

In the current retrospective study, we consecutively included 1654 patients who underwent initial coronary angiography for highly suspected CAD, including chest pain with typical change in ECG or severe lesion in coronary CT angiography screening at Guangdong Provincial People's Hospital from September 2014 to September 2015. Information on demographic characteristics, comorbidities (hypertension, diabetes, stroke, and chronic kidney disease), health behaviors, laboratory results, and carotid ultrasound examinations was retrieved from electronic medical records. Serum UA was measured on admission, and patients were divided into two groups based on serum UA cutoff level of 6.8 mg/dL as previously reported [22,23]. A total of 186 patients without UA data, 10 patients without HDL-C data, and 21 patients without information from carotid ultrasonography examination were excluded (Fig. 1). This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital, and all patients provided their verbal informed consent.

2.2. Carotid atherosclerosis assessment

Experienced sonographers who were unaware of participants' baseline information manually performed carotid ultrasonography examination on a day close to the day of blood sample analysis, using a GE Vivid E95 (GE Healthcare, Milwaukee, WI, USA) and 7.5–12 MHz phased array probe.

The region of interest for cIMT measurement was on the far wall of the bilateral common carotid arteries about 10 mm proximal to the carotid bifurcation. cIMT was defined as the distance between the interface of the lumen–intima and media–adventitia. The mean cIMT was taken as the average of the cIMT values of the left and right carotid arteries. The maximum cIMT was taken as the larger cIMT value between the left and right carotid arteries. Abnormal cIMT was defined as the mean cIMT or the maximum cIMT value $\geq$ 1 mm [24,25]. Carotid artery plaque was also assessed at three different locations, including the common carotid artery, carotid bifurcation, and internal carotid artery on both the left and the right sides. Carotid artery plaque was defined as a focal structure that encroaches into the arterial lumen at least 0.5 mm or 50% of the surrounding cIMT value, or demonstrates a thickness >1.5 mm as measured from the media–adventitia interface to the intima–lumen interface [26]. Carotid plaque score was calculated as the sum of the thickest plaque values on the left and the right sides.

Carotid atherosclerosis was defined as abnormal cIMT and/or presence of carotid artery plaque [26–28]. Two sonographers measured the cIMT and carotid artery plaque and determined the final results together. If there was

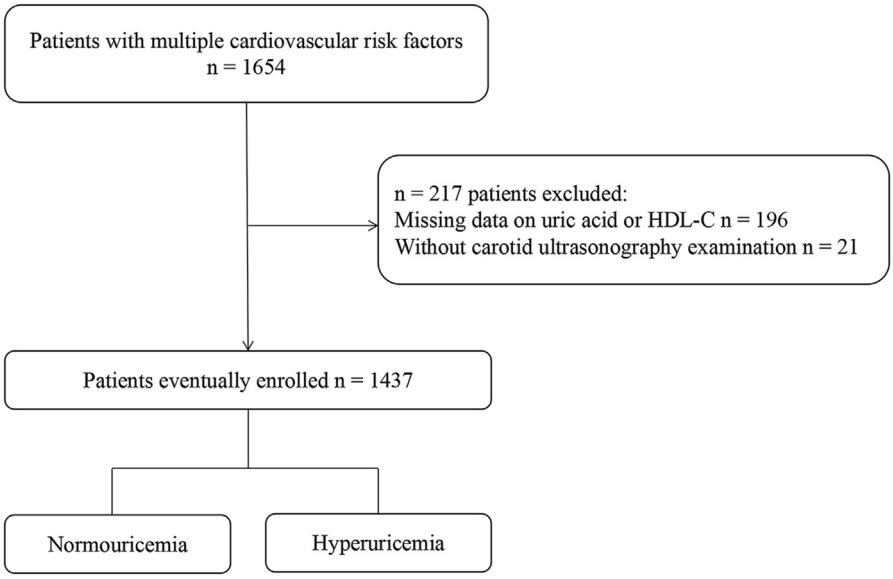

Figure 1 Flow chart of the study.

any discrepancy, a third sonographer was consulted, and the final results were determined through discussion.

2.3. Laboratory examination

Blood cell counts were analyzed using the Sysmex-XE5000 via impedance technology. UA, HDL-C, LDL-C, total cholesterol (TC), triglyceride (TG), and creatinine levels were measured using a Beckman AU5800 spectrophotometer via colorimetry or immunoturbidimetry. C-reactive protein (CRP) was measured by dry chemistry method using the Vitros 250 Chemistry System.

2.4. Covariates

Hypertension was diagnosed in accordance with the European Society of Cardiology guidelines as systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg, which is equivalent to a 24-h ambulatory blood pressure monitoring average of $\geq$130/80 mm Hg, or a home blood pressure monitoring average of $\geq$135/85 mm Hg for two measurements over at least 3 days [29]. Diabetes mellitus (DM) was diagnosed based on fasting blood glucose $\geq$7.0 mmol/L (126 mg/dL) and hemoglobin A1c $\geq$ 6.5% or positive oral glucose tolerance test (2-h plasma glucose $\geq$11.1 mmol/L [200 mg/dL]) or random plasma glucose $\geq$11.1 mmol/L (200 mg/dL) in accordance with the European Society of Cardiology guidelines [30]. Smoking was defined as previous smoking, and alcohol consumption was defined as previous drinking habit.

2.5. Statistical analysis

First, Student's *t*-test for normally distributed data, the Mann–Whitney *U* test for skewed data, and the chi-square test/Fisher's exact test for categorical variables were used to identify significant differences between the two groups. Second, both mean and maximum cIMT were categorized into two groups (abnormal versus normal), while carotid artery plaque was categorized into two groups (yes versus no), according to pre-specified condition. Logistic regression model was used to simultaneously show the results of different adjusted models to evaluate the association between HDL-C and carotid atherosclerosis (abnormal cIMT and carotid artery plaque) at different levels of UA by odds ratio (OR) and 95% confidence intervals (95% CI). In this step, we performed four logistic regression models: model 1 was unadjusted; model 2 was adjusted for age and sex; model 3 was further adjusted for hypertension, diabetes, smoking, and alcohol consumption; model 4 was further adjusted for white blood cell (WBC) count, platelet count, and creatinine level. ORs and 95% CIs were derived from restricted cubic spline regression, with knots placed at the 25th, 50th, 75th, and 95th percentiles of the distribution of HbA1c/HDL-C ratio. The reference value of the HbA1c/HDL-C ratio was the minimum of the group. Third, generalized additive model analysis was used to evaluate the relationship between HDL-C and inflammatory markers (WBC count, neutrophil count, and CRP level) at different levels of UA. Fourth, we performed sensitivity analysis to evaluate the effect of UA on the relationship between HDL-C and carotid atherosclerosis taking into consideration of sex difference. As previously studies reported [31,32], we redefined hyperuricemia as UA level $\geq$7 mg/dL in men and $\geq$6 mg/dL in women for sensitivity analysis. And we also tested the relation between HDL-C and carotid atherosclerosis at different serum UA levels among: patients at risk of residual cardiovascular events (with optimal LDL-C level $<$1.8 mmol/L; n = 313); patients with previous UA-lowering drugs or statins drug use (n = 533). Associations with $P < 0.05$ (two-sided) were considered statistically significant. The analyses were performed using Stata 15.0 (StataCorp LLC, College Station, TX, USA), R version 3.6.1 (The R Project for Statistical

Computing, Vienna, Austria), and EmpowerStats (X&Y Solutions, Inc., Boston, MA, USA).

3. Results

3.1. Study population

A total of 1437 patients with multiple cardiovascular risk factors (992 men and 445 women) were included in the study. The mean age (SD) was 63 (10) years for normouricemia group and 64 (11) for hyperuricemia group. The baseline characteristics of the study participants according to UA level ($\geq$ or $<$6.8 mg/dL) are shown in Table 1. Compared with patients in the normouricemia group, those with hyperuricemia were more likely to be men; to have hypertension or chronic kidney disease; to smoke or consume alcohol; to have higher WBC count and levels of CRP, TG, and creatinine, but lower level of HDL-C. And there was more exposure to diuretic and urate lowering therapy in hyperuricemia than in normouricemia.

3.2. The effect of UA on the relationship between HDL-C and carotid atherosclerosis

In Table 2, the logistic regression models showed that HDL-C levels were associated with abnormal cIMT and presence of carotid artery plaque in the crude model (for abnormal mean cIMT, OR [95% CI]: 0.48 [0.30–0.75]; for abnormal maximum cIMT, OR [95% CI]: 0.49 [0.31–0.78]; for carotid artery plaque, OR [95% CI]: 0.47 [0.28–0.79]). After adjusting for covariates (age, gender, history of hypertension, history of diabetes, smoking, alcohol consumption, WBC counts, platelet count, and creatinine level), the association between HDL-C and carotid atherosclerosis still remained significant among different models in patients with normouricemia (for abnormal mean cIMT, OR [95% CI]: 0.55 [0.33–0.92]; for abnormal maximum cIMT, OR [95% CI]: 0.59 [0.35–1.00]; for carotid artery plaque, OR [95% CI]: 0.53 [0.29–0.94]. However, in patients with hyperuricemia, the association between HDL-C and carotid atherosclerosis was not significant (Table 2). Restricted cubic spline curves indicated that, for patients with normouricemia, there were decreasing trends in the mean cIMT, the maximum cIMT, and the occurrence of carotid artery plaque as HDL-C levels increased, showing the effect of HDL-C against carotid atherosclerosis. However, this effect was not obvious in patients with hyperuricemia (Fig. 2).

3.3. The association between serum uric acid and inflammatory marker

WBC count, neutrophil count, and CRP level on admission were higher in patients with hyperuricemia than in those with normouricemia. As shown in Fig. 3, in normouricemia group, there was a negative correlation between HDL-C and each of these three indicators, whereas in hyperuricemia group, the relationship between HDL-C and each of these three inflammatory indicators weakened.

Table 1 Baseline information.

	Normouricemia n = 932	Hyperuricemia n = 505	P value
Age, years	63 ± 10	64 ± 11	0.216
Male sex	587 (62.98%)	405 (80.20%)	<0.001
Hypertension	508 (54.51%)	329 (65.15%)	<0.001
Diabetes	277 (29.72%)	140 (27.72%)	0.426
Chronic kidney disease	15 (1.62%)	37 (7.40%)	<0.001
Gout	4 (0.43%)	17 (3.37%)	<0.001
Alcohol consumption	40 (4.31%)	38 (7.60%)	0.009
Smoking	293 (31.44%)	194 (38.42%)	0.008
WBC, $\times 10^9$/L	7.28 ± 2.08	7.74 ± 2.34	<0.001
Hemoglobin, g/L	132.43 ± 15.05	131.73 ± 19.04	0.447
Platelets, $\times 10^9$/L	219.33 ± 62.36	220.24 ± 67.83	0.798
Neutrophil ratio, %	60 ± 10	61 ± 11	0.086
CRP, mg/L[a]	9.99 ± 30.26	10.93 ± 25.11	<0.001
TG, mmol/L	1.53 ± 1.19	1.76 ± 1.21	<0.001
TC, mmol/L	4.44 ± 1.21	4.45 ± 1.23	0.874
LDL-C, mmol/L	2.58 ± 1.04	2.62 ± 1.06	0.564
HDL-C, mmol/L	1.11 ± 0.29	1.02 ± 0.25	<0.001
Creatinine, μmol/L	80.23 ± 40.98	113.81 ± 82.81	<0.001
Mean cIMT	1.00 (0.80–1.10)	1.00 (0.80–1.10)	0.798
Maximum cIMT	1.00 (0.80–1.10)	1.00 (0.88–1.10)	0.935
Carotid plaque score	3.30 (1.30–4.62)	3.50 (1.40–4.70)	0.446
Medication history			
ACEI/ARB	149 (15.99%)	82 (16.24%)	0.902
β-blocker	152 (16.31%)	87 (17.23%)	0.655
CCB	126 (13.52%)	71 (14.06%)	0.776
Diuretic	18 (1.93%)	39 (7.72%)	<0.001
Statin	336 (36.09%)	184 (36.44%)	0.897
Urate lowering therapy[b]	6 (0.64%)	23 (4.55%)	<0.001

Data are shown as mean ± SD or median (Q1–Q3) or N (%).
WBC: white blood cell; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium calcium entry blocker.
[a] Missing data are interpolated by median.
[b] Urate lowering therapy includes allopurinol, benzbromarone, Febuxostat.

3.4. Sensitivity analysis

We also conducted sensitivity analysis to evaluate the relationship of HDL-C and carotid atherosclerosis in the setting of different uric acid level in the subsample of patients with optimal LDL-C levels (n = 313). After multivariate adjustment for the covariates included in model 4, in patients with normouricemia, the increase of HDL-C negatively correlated with the occurrence of carotid atherosclerosis (Supplementary Table 1), while the relationship was not significant in those with hyperuricemia. Restricted cubic spline curves also indicated that in patients with hyperuricemia, the effect of HDL-C against atherosclerosis was diminished (Supplementary Fig. 1).

In the sensitivity analysis with redefinition of hyperuricemia in different sex [31,32], we observed similar

Table 2 Odds ratios (95% CIs) of abnormal cIMT or carotid artery plaque according to the concentration of HDL-C at different levels of serum uric acid.

	Normouricemia n = 932				Hyperuricemia n = 505			
	Model 1[a]	Model 2[a]	Model 3[a]	Model 4[a]	Model 1[a]	Model 2[a]	Model 3[a]	Model 4[a]
Abnormal mean cIMT (≥1 mm)								
OR	0.48	0.46	0.56	0.55	0.78	0.68	0.87	0.82
95% CI	0.30–0.75	0.28–0.75	0.33–0.93	0.33–0.92	0.39–1.56	0.32–1.39	0.41–1.84	0.38–1.75
P value	0.001	0.002	0.025	0.024	0.482	0.278	0.709	0.610
Abnormal maximum cIMT (≥1 mm)								
OR	0.49	0.48	0.60	0.59	0.55	0.42	0.56	0.53
95% CI	0.31–0.78	0.29–0.79	0.35–1.01	0.35–1.00	0.27–1.11	0.20–0.89	0.26–1.20	0.24–1.15
P value	0.002	0.004	0.053	0.050	0.097	0.024	0.137	0.109
Carotid artery plaque								
OR	0.47	0.44	0.52	0.53	1.24	0.82	0.99	1.03
95% CI	0.28–0.79	0.25–0.77	0.29–0.93	0.29–0.94	0.53–2.89	0.32–2.07	0.38–2.56	0.39–2.68
P value	0.004	0.004	0.027	0.031	0.613	0.674	0.980	0.960

[a] Model 1: Unadjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for model 2 and hypertension, diabetes, smoking, and alcohol consumption; Model 4: Adjusted for model 3 and white blood cell count, platelet count, and creatinine level.

founding to the main results that, HDL-C levels were negatively related to the occurrence of carotid atherosclerosis after multivariable adjustment in normouricemia group, while not in hyperuricemia group (Supplementary Table 2).

Considering the effect of drugs on the association between HDL-C and carotid atherosclerosis, we performed another analysis in a subsample of patients with UA-lowering drugs or statins. As shown in Supplementary Table 3, the association between HDL-C and abnormal cIMT remained significant among different models in patients with normouricemia but not in hyperuricemia, which was consistent with our main results. However, we found the association between HDL-C and the presence of carotid artery plaque in normouricemia was not significant.

4. Discussion

The present study analyzed the effect of serum UA level on the relationship between HDL-C and carotid atherosclerosis in patients with high risk of ASCVD. We found that an elevated serum UA level was able to impact the role of HDL-C on carotid atherosclerosis and potentially affect the relationship between HDL-C and inflammation markers in these patients. Furthermore, the effect of uric acid on HDL-C–carotid atherosclerosis relationship still remains in the subset of patients with optimal LDL-C level.

It is recognized that HDL-C impacts the cardiovascular system by multiple mechanisms, such as reversing cholesterol transport to reduce atherosclerosis burden [33], antioxidant and anti-inflammatory effects [6], and increasing insulin sensitivity [34]. Significant relationships have been reported between hyperuricemia and surrogate markers of atherosclerosis, such as inflammation markers [4,35], oxidative stress markers [36] and endothelial dysfunction [37]. HDL-C and hyperuricemia have the opposite effect on the cardiovascular system [8,9], but the interaction between UA and HDL-C is still not fully clarified. Liu et al. [38] studied the relationship among UA, HDL-C, and ASCVD mortality, and found that as the UA/HDL-C ratio increased, the ASCVD mortality rate increased, which suggested that UA was associated with the effect of HDL-C on the prognosis of ASCVD. Moreover, in a cross-sectional study with 1503 participants [10], an elevated serum UA level was found to mark a proinflammatory state and was strongly associated with HDL-C dysfunction. In contrast, in a five-year prospective cohort study that enrolled healthy participants without ASCVD risk factors, Kuwabara et al. [12] observed that an increased serum UA level was not an independent risk factor for low HDL-C. The results of our study indicated that HDL-C and hyperuricemia play opposing roles in the atherosclerosis process, and possibly this relationship would be truly reflected in patients with high risk of ASCVD. In the subsample of patients using UA-lowering drugs or statins, we could not find the association between HDL-C and the presence of carotid artery plaque in normouricemia group. Since previous studies indicated that the use of statins possibly affected the levels of HDL-C as well as the carotid artery plaque volume and most of the patients in this subsample used statins [39,40], we considered that statins use may interference the association between HDL-C and the presence of carotid artery plaque.

UA causes atherosclerosis by increasing inflammatory response and oxidative stress. In a randomized clinical trial involving 176 patients with type 2 DM and asymptomatic hyperuricemia, urate lowering therapy significantly reduced serum high-sensitivity CRP levels and cIMT to inhibit the progression of atherosclerosis [41]. The effect of lowering UA levels on preventing atherosclerosis may be achieved by weakening the inflammatory response. Atherosclerosis is an inflammatory process mediated by cytokine production and vascular regulatory mechanisms [42]. Previous studies [4,35,43,44] found that UA was able to stimulate the production of inflammatory factor and intercellular adhesion molecule to stimulate downstream inflammation, thereby contributing to the

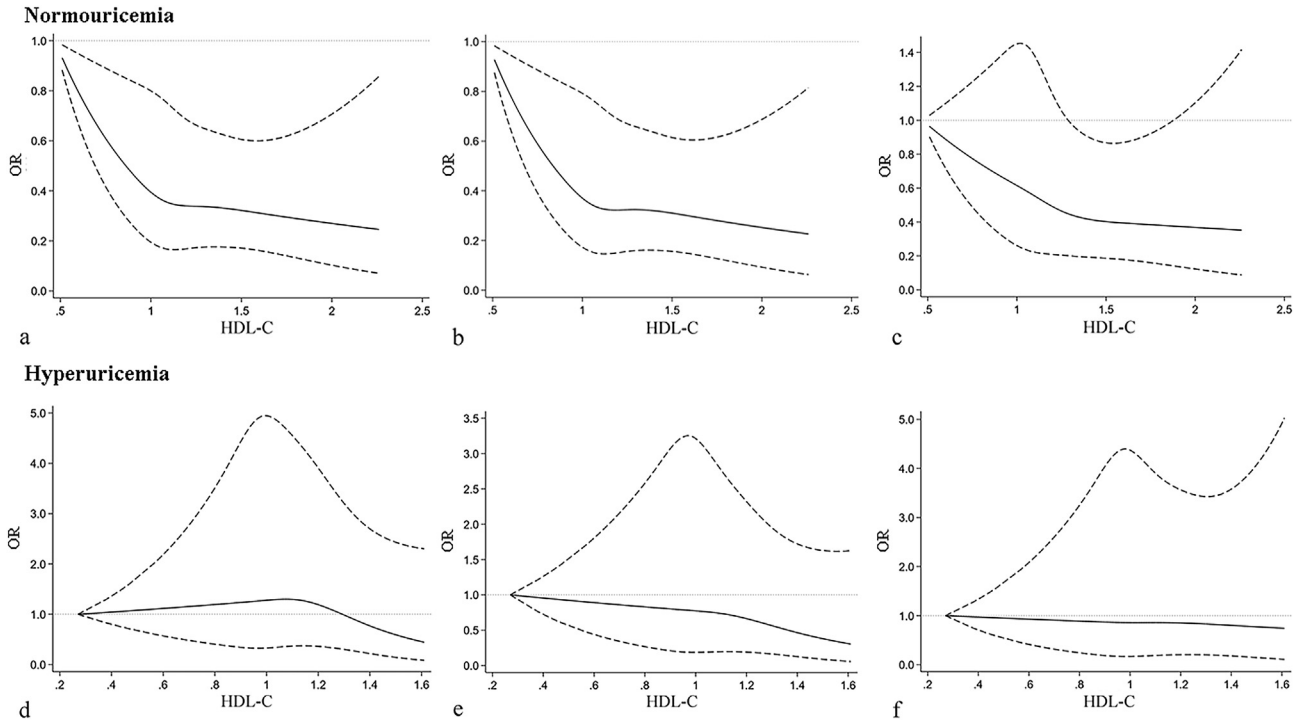

Figure 2 The association between HDL-C and abnormal cIMT or carotid artery plaque at different levels of serum uric acid. a. HDL-C and abnormal mean cIMT in normouricemia; b. HDL-C and abnormal maximum cIMT in normouricemia; c. HDL-C and carotid artery plaque in normouricemia; d. HDL-C and abnormal mean cIMT in hyperuricemia; e. HDL-C and abnormal maximum cIMT in hyperuricemia; f. HDL-C and carotid artery plaque in hyperuricemia. In the hyperuricemia group, the highest 2% of participants (n = 10) are not shown in the figures for small sample sizes with large 95% CI.

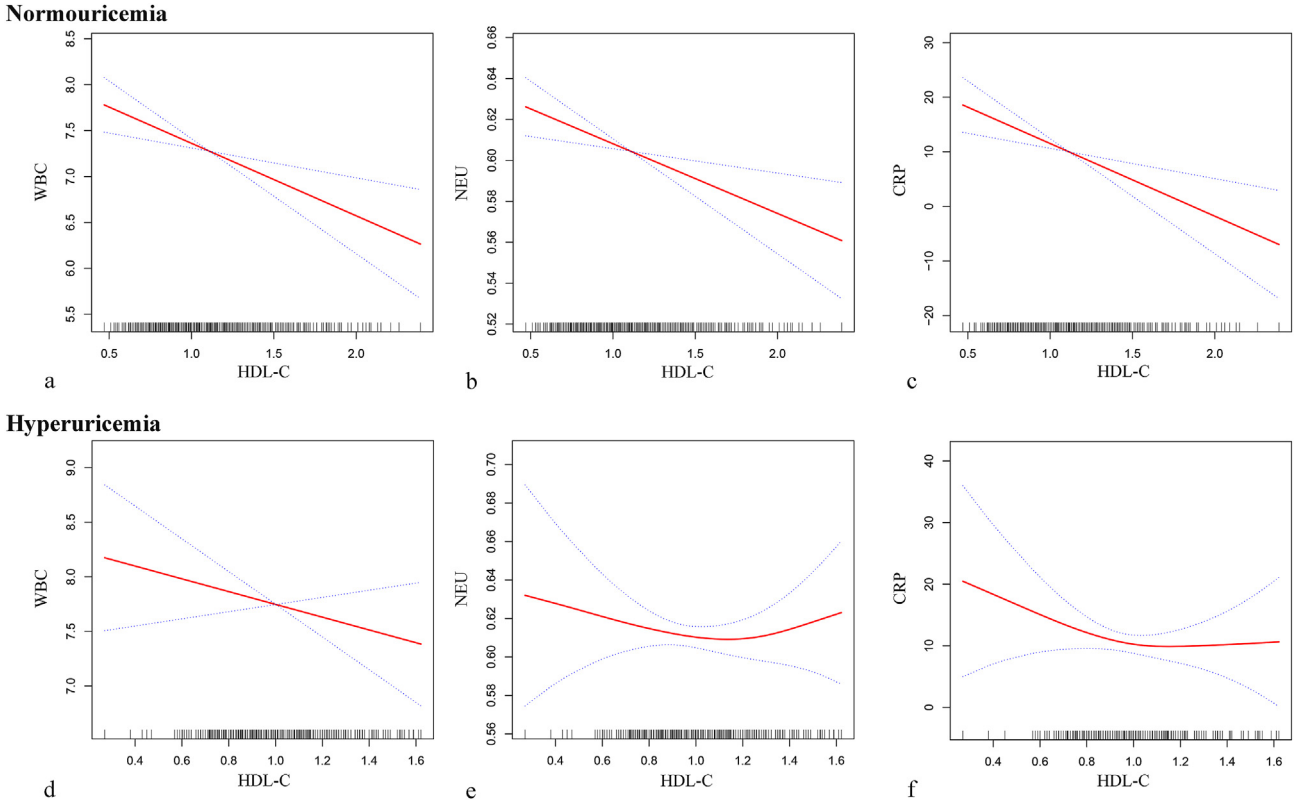

Figure 3 The association between HDL-C and different inflammatory markers at different levels of serum UA. a. HDL-C and WBC in normouricemia; b. HDL-C and NEU in normouricemia; c. HDL-C and CRP in normouricemia; d. HDL-C and WBC in hyperuricemia; e. HDL-C and NEU in hyperuricemia; f. HDL-C and CRP in hyperuricemia.

progression of atherosclerosis. In addition, Kramer et al. [45] treated the mice with uricase gene transfer and xanthine oxidase inhibitors to reduce the UA levels, and found that the decrease in UA levels inhibited atherosclerosis plaque formation. All of these mechanistic studies support our hypothesis that elevated serum UA levels mark pre-inflammatory state and promote the development of atherosclerosis. By analyzing the relationship between HDL-C and inflammatory markers, such as WBC count, neutrophil ratio, and CRP level at different UA levels, our study showed a significant negative correlation between HDL-C and inflammatory markers in normouricemia patients, while the negative correlation was weaker and even became positive in patients with hyperuricemia. Our results are consistent with previous findings and further illustrate the possible mechanism by which UA levels affect the association between HDL-C and carotid atherosclerosis.

The multifactorial effect of risk factors is now the front topic of ASCVD. Wijnands et al. [46] found that a UA level increase of 1 SD (81 μmol/L) was associated with a 0.024-mm increase in cIMT. A negative correlation between HDL-C and ASCVD has been consistently reported in observational studies, which was noted in the 2019 ESC/EAS guidelines for the management of dyslipidemias [47]. As for the association between HDL-C and ASCVD, our study further explored the effect of UA and found that the effects of HDL-C on carotid atherosclerosis differed at different UA levels. In addition, for patients at high risk of ASCVD, the guidelines recommend that the optimal control of LDL-C is $\geq$ 50% reduction from baseline or $<$1.8 mmol/L ($<$70 mg/dL) [47]. In the present study, the effect of serum UA on the role of HDL-C in carotid atherosclerosis remained in patients with optimal LDL-C level ($<$1.8 mmol/L), thereby supporting the consistent interaction between UA and HDL-C in preventing ASCVD. Besides, the relationship between hyperuricemia and metabolic syndrome (MetS) also gradually attracted our attention. Cicero et al. found that MetS was more common at high serum UA levels through the historical cohort of the Brisighella Heart Study [48]. Pugliese et al. emphasized the importance of incorporating SUA into MetS when assessing clinical cardiovascular outcomes [49]. These findings indicated that understanding the complex relationship between UA and other risk factors is critical for the prevention of atherosclerosis. Our results are significant for further exploring the possible mechanisms of the interaction between UA and HDL-C in ASCVD, and contribute to understanding of the relationship among multiple risk factors of ASCVD.

Several limitations should be considered. First, our study was a cross-sectional study and could not determine the causal relationship between UA levels and further weakened the association between HDL-C and carotid atherosclerosis, given that it did not measure the effect of elevated UA levels over time. However, we explored the relationship among these factors, paving the way for future research. Second, the majority of the population included in this study was Chinese, meaning that our conclusions might not necessarily be applicable for other ethnic populations.

5. Conclusion

In the present study, we explored the effect of HDL-C on carotid atherosclerosis at different serum UA levels. Hyperuricemia marks a pre-inflammatory state and impacts the association between HDL-C and carotid atherosclerosis. Our study has important clinical implications for better understanding of the multifactorial effects in the development of atherosclerosis. The effective control of serum UA is an important target for the prevention of atherosclerosis.

Author contributions

XMH and JLL contributed to the manuscript preparation; WL and CYW contributed to the data collection and collation. XMH contributed to the data analysis. GL provided critical revisions of the manuscript. YLZ and HJD contributed to the research ideas and approved the final version of the manuscript for submission.

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Declaration of competing interest

The authors declare no conflicts of interest related to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.03.026.

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