Contribution of Nontraditional Lipid Profiles to Hyperuricemia in a Hypertensive Population: Findings from the China Hypertension Registry Study

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Research

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Abstract

Background: Current studies support nontraditional lipid profiles [total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio, triglyceride (TG)/HDL-C ratio, low-density lipoprotein cholesterol (LDL -C)/HDL-C ratio, non-high-density lipoprotein cholesterol (non-HDL-C)] as reliable indicators of cardiovascular disease, stroke and diabetes. However, whether nontraditional lipid profiles can be used as reliable markers for hyperuricemia (HUA) remains unclear due to limited research. The present study investigated the relationship of nontraditional lipid profiles with HUA in hypertensive patients.

Methods: We analyzed data from 13,721 Chinese hypertensive population untreated with lipid-lowering drugs. The relationship between non-traditional lipid profiles and HUA was examined by multivariate logistic regression analysis and smooth curve fitting (penalized spline method).

Results: The results showed that there were positive associations of TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C with HUA, respectively (all P<0.001). Furthermore, nontraditional lipid profiles were converted from continuous variables to tertiles. Compared with lowest tertile, the multivariate adjusted ORs (95% CI) of TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio and non-HDL-C in highest tertile were 1.79 (1.62, 1.99), 2.09 (1.88, 2.32), 1.67 (1.51, 1.86), 1.93 (1.74, 2.13), respectively (all P<0.001).

Conclusions: In Chinese hypertensive population, there were positive associations between nontraditional lipid profiles (TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C) and HUA. Our findings further expand the scope of application of nontraditional lipid profiles. These novel and important results suggest that nontraditional lipid profiles can be used as potential and valuable indicators of HUA, and provide a new strategy for the prevention and treatment of HUA.

Background

Hyperuricemia (HUA) is a metabolic abnormality syndrome caused by disorders of purine metabolism[1]. Previous studies have shown that HUA is an independent risk factor for metabolic syndrome, chronic kidney disease (CKD), hypertension, cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and death[2, 3]. Epidemiological studies show that the overall prevalence of HUA in China was 13.3%[4], and the prevalence of HUA was significantly higher in hypertensive patients[5]. The dramatically increasing prevalence of HUA is a great challenge to public health concerns and constitutes a serious socioeconomic burden[6]. Hence, identifying HUA-related risk factors in hypertension population and finding potential valuable indicators, could help to improve the management and treatment strategy of chronic diseases.

Previous studies have reported that HUA was associated with higher levels of TC, TG and LDL-C, and lower levels of HDL-C[7, 8]. However, the fact is that most HUA patients usually have multiple disorders of lipid metabolism[9, 10], so a single lipid may not be an effective indicator of HUA. Recently, there is increasing evidences that nontraditional lipid profiles, represented TC/HDL-C ratio, TG/HDL-C ratio, LDL-

C/HDL-C ratio, and non-HDL-C, are valuable and excellent markers of CVD, T2DM, CKD and all-cause mortality[11–14]. HUA, as an independent risk factor for CKD, CVD and all-cause mortality, plays an important role in the occurrence and progression of these diseases[15, 16]. Therefore, there may be relationships between nontraditional lipid profiles and HUA. However, to date, there is limited information on the association between these four nontraditional lipid profiles and HUA in Chinese population. In addition, more than 1/3 of hypertensive patients have HUA, and these two diseases have a synergistic effect on the occurrence and development of CVD and death[17, 18]. Therefore, the present study aims to investigate the independent relationships between four nontraditional lipids profiles and HUA in Chinese hypertensive population.

Materials And Methods

Study design and participants

The study data were drawn from the China Hypertension Registry Study (http://www.chictr.org.cn/, No: ChiCTR1800017274). Details of the methodology, primary objectives, inclusion and exclusion criteria for this study had been described in detail elsewhere [19]. Briefly, this study was a large observational cohort study of hypertensive patients. Hypertension was defined as office Systolic blood pressure (SBP) values ≥ 140 mmHg and/or diastolic BP (DBP) values ≥ 90 mmHg, self-report history of hypertension, or the use of antihypertensive drug(s) at baseline[20]. From March to August 2018, a total of 14,268 patients with hypertension were recruited into our study in Wuyuan, Jiangxi Province, China, and all study participants signed informed consent before being recruited into the study. We excluded participants taking lipid-lowering drugs and finally analyzed data from 13,721 hypertensive patients. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute (No. CH1059).

Data collection

All study participants were required to collect fasting, venous blood samples by trained study staff during the baseline data collection period. Total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), serum uric acid (SUA, μmol/L), estimated glomerular filtration rate (eGFR, ml/min/1.73 m2), homocysteine (Hcy, μmol/L) and fasting blood glucose (FBG, mmol/L) were measured by an automatic clinical analyzer (Beckman Coulter, USA) in Biaojia Biotechnology Laboratory, Shenzhen, China. Body mass index (BMI, kg/m2) was calculated by dividing weight by the square of height. Blood pressure (BP, mmHg) was measured by electronic sphygmomanometers after the subjects had rested for 10 min. Other covariates were obtained through questionnaires, including age, sex, current smoking, alcohol consumption, history of disease (including stroke, CHD and diabetes), and drug history (including antihypertensive drugs, lipid-lowering drugs and glucose-lowering drugs).

Definition of nontraditional lipid profiles and HUA

The nontraditional lipid profiles represented TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio and non-HDL-C[13, 14, 21, 22]. The TC/HDL-C, TG/HDL-C and LDL-C/HDL-C ratios were calculated as TC, TG, LDL-C divided by HDL-C, respectively. Non-HDL-C was calculated as HDL-C subtracted from TC. To date, eight guideline documents recommended that serum uric acid level >420 μmol/L (7 mg/dL) was diagnosed as HUA, regardless of sex[23-25]. According to the updated Chinese guidelines, HUA in our study was defined as serum uric acid level >420 μmol/L (7 mg/dL), regardless of gender[25].

Statistical analysis

Baseline characteristics of the study population were displayed according to with or without HUA. Continuous variables are presented as the mean ± SD and categorical variables are presented as percentage (%). Logistic regression analyses were performed to assess the association of nontraditional lipid profiles (TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C) with HUA by presenting the odds ratio (OR) and 95% confidence interval (CI) after adjusting for confounding factors. The trend test was used to evaluate the linear relationship between nontraditional lipid profiles and HUA, when nontraditional lipid profiles used as tertiles. Fully adjusted smoothing curve fitting (penalized spline method) visually demonstrated the relationship between nontraditional lipid profiles and HUA.

All statistical analyses were performed using the statistical package R (http://www.R-project.org, -e R Foundation) and Empower (R) (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). Statistical significance was defined as two-tailed $P < 0.05$.

Results

Baseline characteristics of the study participants

A total of 13,721 hypertensive patients untreated lipid-lowering drugs were included in our analysis (mean age: 63.79 ± 9.41 years; 47.23% males) (Fig. 1). The distributions of study participant baseline characteristics according to the status of HUA (non-HUA and HUA) were presented in Table 1. Compare with non-HUA group, HUA group had higher values for age, male, current smoking, alcohol use, CHD, diabetes mellitus, antihypertensive drugs, BMI, DBP, TC, TG, LDL-C, TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, non-HDL-C, Hcy and FBG, and lower values for SBP, HDL-C and eGFR (all $P < 0.05$).

Table 1
Characteristics of Study Population

Variables*	Total (n = 13,721)	non-HUA (n = 7,622)	HUA (n = 6,099)	*P* value
Demographics				
Age, years	63.79 ± 9.41	63.56 ± 9.02	64.08 ± 9.87	0.002
Male,	6,484 (47.23)	2,525 (33.13)	3,954 (64.83)	< 0.001
Current smoking, %	3,568 (26.00)	1,578 (20.71)	1,987 (32.58)	< 0.001
Alcohol use, %	3,010 (21.93)	1,206 (15.83)	1,801 (29.53)	< 0.001
Comorbidity, %				
Stroke	820 (5.97)	450 (5.90)	370 (6.07)	0.69
CHD	633 (4.61)	321 (4.21)	312 (5.12)	0.012
Diabetes mellitus	2,438 (17.76)	1,250 (16.40)	1,187 (19.46)	< 0.001
Medication use, %				
Antihypertensive drugs	8,788 (64.03)	4,725 (62.01)	4,059 (66.56)	< 0.001
Glucose-lowering drugs	662 (4.82)	361 (4.74)	300 (4.92)	0.62
Physical examination				
BMI, kg/m^2	23.57 ± 3.75	23.25 ± 3.82	23.98 ± 3.61	< 0.001
SBP, mmHg	148.54 ± 17.82	149.45 ± 17.31	147.39 ± 18.39	< 0.001
DBP, mmHg	89.04 ± 10.76	88.75 ± 10.39	89.40 ± 11.20	< 0.001
Laboratory results				
TC, mmol/L	5.18 ± 1.10	5.13 ± 1.06	5.24 ± 1.15	< 0.001
TG, mmol/L	1.80 ± 1.25	1.64 ± 1.04	1.99 ± 1.44	< 0.001
LDL-C, mmol/L	3.00 ± 0.80	2.96 ± 0.78	3.05 ± 0.83	< 0.001
HDL-C, mmol/L	1.57 ± 0.43	1.60 ± 0.43	1.53 ± 0.42	< 0.001
TC/HDL-C ratio	3.44 ± 0.87	3.33 ± 0.81	3.58 ± 0.92	< 0.001
TG/HDL-C ratio	1.31 ± 1.27	1.16 ± 1.04	1.50 ± 1.48	< 0.001

Abbreviations: CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Hcy, homocysteine; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate.

*Data are presented as number (%) or mean ± standard deviation.

Variables*	Total (n = 13,721)	non-HUA (n = 7,622)	HUA (n = 6,099)	*P* value
LDL-C/HDL-C ratio	2.01 ± 0.65	1.94 ± 0.62	2.10 ± 0.69	< 0.001
non-HDL-C, mmol/L	3.61 ± 0.99	3.53 ± 0.93	3.71 ± 1.04	< 0.001
Hcy, μmol/L	17.96 ± 11.03	16.28 ± 9.23	20.06 ± 12.63	< 0.001
FBG, mmol/L	6.17 ± 1.59	6.14 ± 1.68	6.20 ± 1.47	0.027
eGFR, ml/min/1.73 m^2	88.33 ± 20.19	94.68 ± 16.05	80.40 ± 21.95	< 0.001

Abbreviations: CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Hcy, homocysteine; FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate.

*Data are presented as number (%) or mean ± standard deviation.

Relationship between nontraditional lipid profiles and HUA

Fig. 2 showed the results of smooth curves between four nontraditional lipids profiles and HUA. Fig. 2A, 2B, 2C and 2D showed the positive associations of TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio and non-HDL-C with HUA, respectively.

Table 2 showed the results of multiple logistic regression analysis of the relationship between nontraditional lipid profiles and HUA. In the crude and adjusted model, there were positive associations of TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C with HUA, respectively (all P <0.001). After adjusting for all variables, an increment of 1 SD in TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C was associated with greater ORs (95% CI) of 1.36 (1.29, 1.43), 1.28 (1.23, 1.33), 1.42 (1.33, 1.51), and 1.35 (1.30, 1.41) for HUA, respectively (all P <0.001). Furthermore, nontraditional lipid profiles were converted from continuous variables to tertiles. Compared with group T1, the multivariate adjusted ORs (95% CI) of TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio and non-HDL-C in group T3 were 1.79 (1.62, 1.99), 2.09 (1.88, 2.32), 1.67 (1.51, 1.86), 1.93 (1.74, 2.13), respectively (all P <0.001). All P for trend <0.001 indicated the associations between four nontraditional lipid profiles and HUA were likely to be linear.

Table 2.

Odd ratios (95% CI) for HUA according to continuous and tertiles of nontraditional lipid profiles

			Crude model		Adjusted model	
Variables	N	Events, n (%)	OR (95%CI)	*P* value	OR (95%CI)	*P* value
TC/HDL-C ratio (Per 1 SD increase)	13,721	6,099 (44.5%)	1.39 (1.33, 1.44)	<0.001	1.36 (1.29, 1.43)	<0.001
Tertiles of TC/HDL-C ratio						
T1 (<2.76)	4,572	1,728 (37.8%)	Reference		Reference	
T2 (2.76-4.13)	4,574	1,954 (42.7%)	1.22 (1.13, 1.33)	<0.001	1.30 (1.18, 1.44)	<0.001
T3 (≥4.13)	4,575	2,417 (52.8%)	1.84 (1.70, 2.00)	<0.001	1.79 (1.62, 1.99)	<0.001
P for trend			<0.001		<0.001	
TG/HDL-C ratio (Per 1 SD increase)	13,721	6,099 (44.5%)	1.27 (1.23, 1.31)	<0.001	1.28 (1.23, 1.33)	<0.001
Tertiles of TG/HDL-C ratio						
T1 (<0.62)	4,571	1,708 (37.4%)	Reference		Reference	
T2 (0.62-2.01)	4,576	1,934 (42.3%)	1.23 (1.13, 1.33)	<0.001	1.30 (1.17, 1.43)	<0.001
T3 (≥2.01)	4,574	2,457 (53.7%)	1.95 (1.79, 2.11)	<0.001	2.09 (1.88, 2.32)	<0.001
P for trend			<0.001		<0.001	
LDL-C/HDL-C ratio (Per 1 SD increase)	13,721	6,099 (44.5%)	1.47 (1.40, 1.55)	<0.001	1.42 (1.33, 1.51)	<0.001
Tertiles of LDL/HDL-C ratio						
T1 (< 1.50)	4,574	1,742 (38.1%)	Reference		Reference	
T2 (1.50-2.53)	4,572	1,967 (43.0%)	1.23 (1.13, 1.33)	<0.001	1.31 (1.18, 1.44)	<0.001
T3 (≥2.53)	4,575	2,390 (52.2%)	1.78 (1.64, 1.93)	<0.001	1.67 (1.51, 1.86)	<0.001
P for trend			<0.001		<0.001	
non-HDL-C (Per 1 SD	13,721	6,099	1.20 (1.16,	<0.001	1.35 (1.30,	<0.001

increase)		(44.5%)	1.25)		1.41)	
Tertiles of non-HDL-C						
T1 (< 2.84)	4,572	1,849 (40.4%)	Reference		Reference	
T2 (2.84-4.37)	4,543	1,945 (42.8%)	1.10 (1.01, 1.20)	0.022	1.31 (1.19, 1.44)	<0.001
T3 (≥4.37)	4,606	2,305 (50.0%)	1.48 (1.36, 1.60)	<0.001	1.93 (1.74, 2.13)	<0.001
P for trend			<0.001		<0.001	

Abbreviations: OR, odd ratio; CI, confidence interval; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Adjusted model: adjusted for age, sex, BMI, SBP, DBP, current smoking, alcohol use, eGFR, Hcy, diabetes mellitus and anti-hypertensive drugs.

Discussion

In this large sample of Chinese hypertensive population, the constellation of our findings offered novel evidence for an independent positive association of nontraditional lipid profiles (TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C) with HUA. Our findings suggest that detection of nontraditional lipid profiles may be beneficial for the prevention and treatment of HUA.

Increasing evidence suggested that nontraditional lipid profiles could be a valuable indicator for a variety of diseases. Guo et al. [13] included 5,782 patients with hypertension (mean age: 57 ± 10 years) for analysis, and found that higher TC/HDL-C, TG/HDL-C and LDL-C/HDL-C ratio were associated with higher risk of ischemic stroke, while non-HDL-C was not associated with ischemic stroke. Wang et al. [22] analyzed data from 3,259 patients with hypertension (mean age: 58.78 ± 10.20 years), and found that nontraditional lipid profiles were positively correlated with reduced eGFR. Wang et al. [21] analyzed data of 10,756 Chinese (mean age: 53.8 years) and found that nontraditional lipid profiles were positively correlated with CVD risk. Wang et al.[14] analyzed the data of 2,944 hypertensive patients (mean age: 57.09 ± 11.29 years), indicating that the nontraditional lipid profiles were significantly positively associated with diabetes, and further found that TG/HDL-C ratio was more significantly correlated with diabetes. Therefore, we have sufficient reasons to believe that nontraditional lipid profiles are effective indicators of these diseases, including stroke, CVD, diabetes, CKD. It is noteworthy that HUA plays an important role in the occurrence and development of the diseases mentioned above[3, 24, 26]. Therefore, prevention and treatment of HUA have great clinical benefits. However, to our knowledge, few studies have explored the relationship between nontraditional lipid profiles and HUA, so it is not clear whether nontraditional lipid profiles can serve as valuable markers of HUA. Our findings extend the application of nontraditional lipids and well fill in the gaps of previous studies, so this study has very important clinical significance.

There is a panel of plausible pathomechanisms responsible for the increased risk of HUA in those with poor nontraditional lipid profiles. It was widely-accepted that reduced renal function, inflammation, insulin resistance (IR), lifestyle and lipid-lowering drugs can induce HUA. Excessive lipids deposit on the intima, and mononuclear macrophages become foam cells by phagocytosis of lipids deposited on the intima, thus causing renal arteriosclerosis, resulting in reduced filtration function of the kidney, and thus reduced excretion of uric acid from the kidney, resulting in HUA production[27]. Higher levels of TC/HDL-C and TG/HDL-C ratio may be mediated by CRP-mediated inflammatory response, leading to the occurrence of HUA[28, 29]. Higher lipids lead to IR through lipotoxicity, inflammation and endoplasmic reticulum stress, which in turn leads to the development of HUA. In addition, some researchers have found that hyperlipidemia and HUA patients share the same lifestyle and diet, such as excessive alcohol consumption and high-fat food intake, which also suggests that clinicians should conduct lipid-lowering and uric acid-lowering treatments simultaneously[30]. Interestingly, Deedwania et al. found that lipid-lowering drugs not only reduced lipid levels, but also reduced SUA in patients with CVD[30]. There was a close relationship between nontraditional lipid profiles and HUA. However, current basic studies cannot fully elucidate the mechanism behind this relationship, and further basic experiments are needed to fully elucidate the specific biological mechanism of this association.

Limitations Of The Study

Our study has obvious strengths and some limitations. This study is currently the first study to examine the association of nontraditional lipid profiles (TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C) with the risk of HUA in Chinese hypertension population. Nevertheless, some limitations should be noted. First, as a cross-sectional study, our results failed to provide causality regarding the relationship between nontraditional lipid profiles and HUA. Second, our study population is from Chinese hypertensive patients, so the generality of our conclusions is limited.

Conclusions

In Chinese hypertensive population, there were positive associations between nontraditional lipid profiles (TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL-C) and HUA. Our findings further expand the scope of application of nontraditional lipid profiles. These novel and important results suggest that nontraditional lipid profiles can be used as potential and valuable indicators of HUA, and provide a new strategy for the prevention and treatment of HUA.

Abbreviations

CKD: Chronic kidney disease; CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; CHD: Coronary heart disease; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; Hcy: Homocysteine; FBG: Fasting blood glucose; Egfr: estimated glomerular filtration rate.

Declarations

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Author contributions

All authors were responsible for drafting the manuscript and revising it critically for constructive intellectual content. All authors approved the version to be published.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Anhui Medical University Biomedical Institute (No. CH1059). Informed written consent was obtained from all patients before their enrollment in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Figures

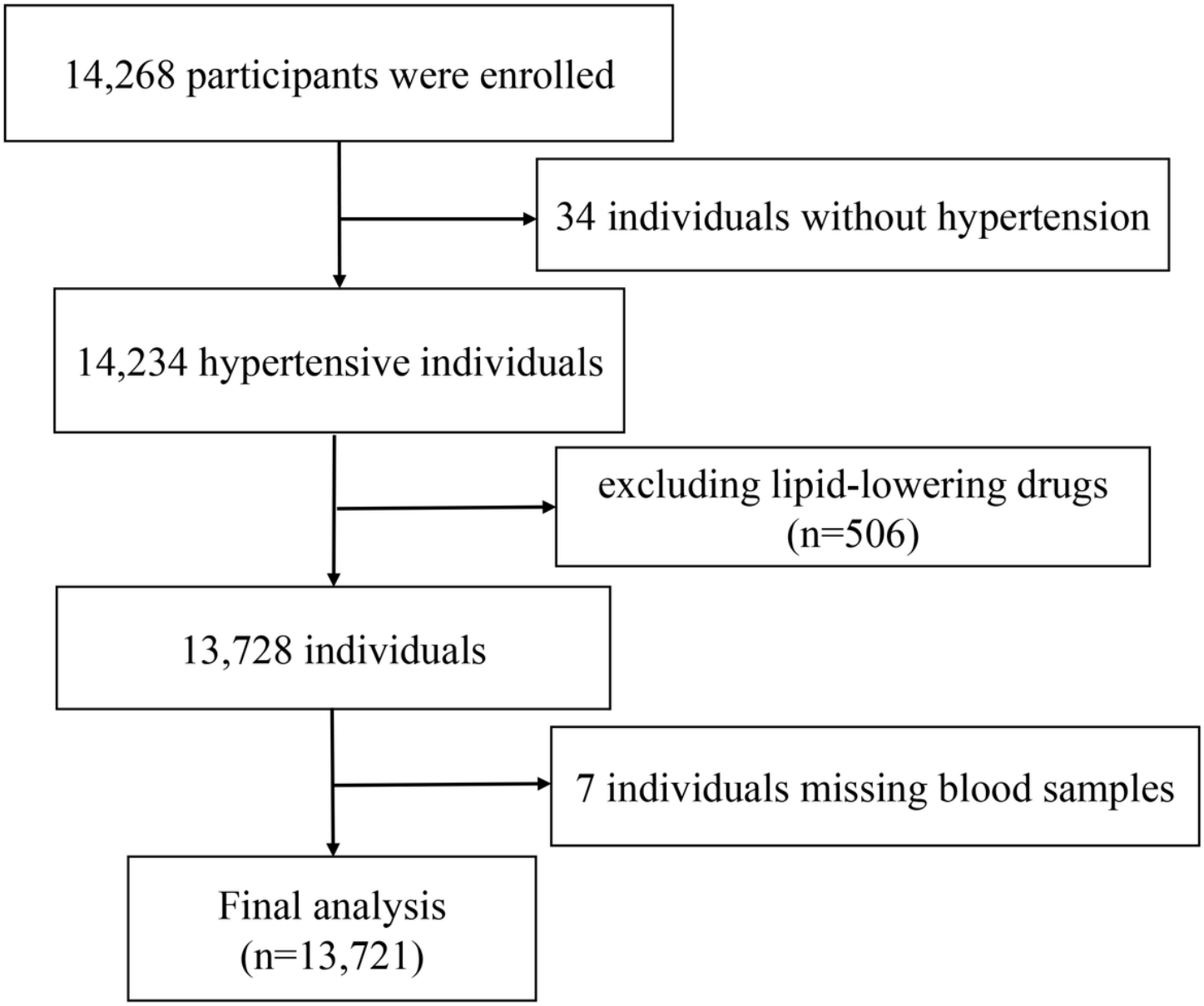

Figure 1

Flow chart of study participants

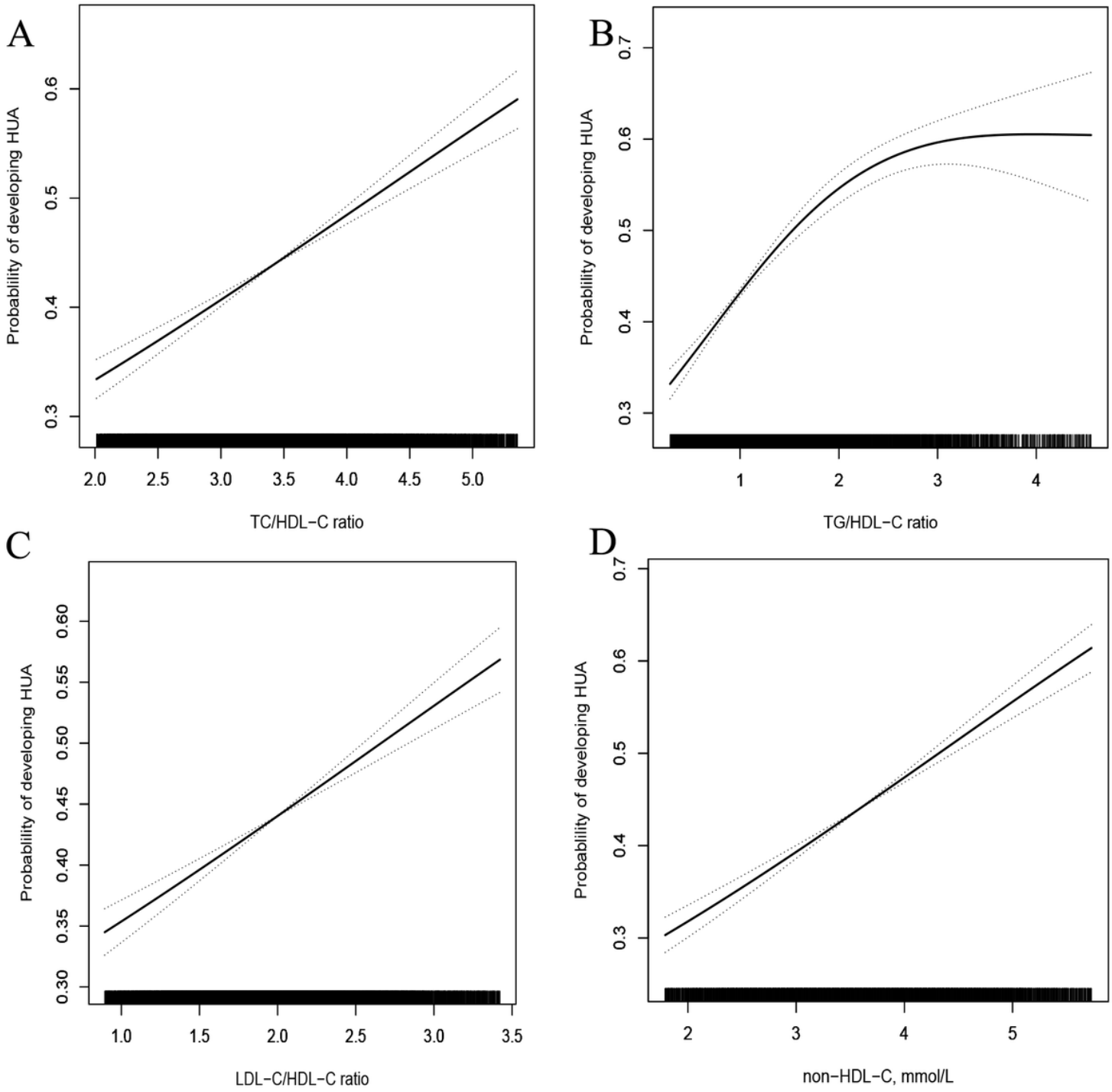

Figure 2

The association between TC/HDL-C (A), TG/HDL-C (B), LDL-C/HDL-C ratio (C), or non-HDL-C (D) and HUA. Adjusted for age, sex, BMI, SBP, DBP, current smoking, alcohol use, eGFR, Hcy, diabetes mellitus and anti-hypertensive drugs.