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High prevalence of hyperuricemia and the impact on non-valvular atrial fibrillation: Results from the Guangzhou Heart Study

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ABSTRACT

Objectives: Epidemiological features of hyperuricemia (HUA) have regional difference. The prevalence of HUA and non-valvular atrial fibrillation (NVAF) in southern China is not reported.

Design: A cross-sectional study.

Setting and participants: A total of 11488 permanent residents aged 35 or above from urban and rural areas of Guangzhou city were enrolled in this study. A questionnaire was used to compile each participant's demographic information and relevant epidemiological factors for HUA and NVAF. A range of blood tests were assessed and single-lead 24 hours ECG was performed for all participants.

Main outcome measures: The criterion of diagnosis of NVAF followed the 2014 AHA/ACC/HRS guideline. HUA was defined as serum uric acid (SUA) >420μmol/L in males and >360μmol/L in females.

Results： The incidence of HUA was 39.6% (44.8% in male and 36.7% in female, respectively) and 144 residents (1.25%) were found with NVAF. Prevalence of HUA of women increased with age but maintained a steady high level in men. After adjusting for potential confounding factors, factors including age, living in urban areas, alcohol consumption, central obesity, elevated fasting plasma glucose, elevated blood pressure, reduced HDL cholesterol and raised triglycerides level were associated with the increased risk of HUA. Residents with HUA had a markedly higher risk of NVAF. According to subgroup analysis separated by sex, the variable of SUA had a modest predictive value of NVAF in females while the value was mild in males.

Conclusions: The prevalence of HUA was extremely high among citizens of southern China. HUA was strongly related to NVAF especially in Chinese females according to our study.

Strengths and limitations of this study:

- The study investigates the prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation.
- This cross-sectional study includes a large cohort from urban and rural areas of Guangzhou.
- The surveyed areas are all randomized to increase reliability.
- This study doesn't include resident under age 35.
- This is a cross-Sectional study and the results need to be further clarified through prospective studies.

INTRODUCTION

The prevalence of hyperuricemia (HUA) ranged from 13.3% to 21.6% and showed sex related difference according to reports from different countries or regions [1, 2]. Regional difference could also be observed in same country, which strongly implied the impact of surrounding, climate, economic state and especially the dietary habits [3, 4]. A number of epidemiologic studies have reported a relation between SUA level and variety cardiovascular conditions such as hypertension, coronary artery disease, vascular dementia, metabolic syndrome, cerebrovascular disease and kidney disease, but the relative association remains controversial according to other studies like Framingham Heart Study which argued that uric acid is not a risk factor for cardiovascular disease [5]. Prevalence of HUA in typical southern China city like Guangzhou has not been reported. As a region with unique dietary habit and climate, prevalence of HUA and its association with cardiovascular disease should provide additional information in this study field.

Atrial fibrillation (AF) has been well known as the most common clinical cardiac arrhythmia which contributes to increased morbidity and mortality especially in those with cardiovascular risk factors [6]. As previously reported, number of AF patients is estimated to rise to 9 million by 2050 in China [7] and the increasing prevalence of AF also makes it a global health problem [8, 9]. The association between AF and HUA has been reported a lot[10], but whether SUA is one of risk factors of AF remains under discussion.

We conducted this cross-sectional population-based study to reveal the prevalence of HUA and its association with non-valvular AF(NVAF) in Guangzhou residents.

Materials and methods

Study population

We conducted a cardiovascular epidemiological survey (the Guangzhou Heart Study) from July 2015 to August 2017 in Guangzhou. Two streets (Dadong Street and Baiyun Street) were randomized selected to stand for urban areas while one street and two towns (Xiaoguwei Street, Xinzao Town and Nancun Town) were chosen as rural areas. A sample of permanent residents aged 35 and above was selected by cluster sampling in each community of the selected areas demonstrated above.

The residents in the study sites were invited to participate in this study by 3-round mobilization via door-to-door visits or telephone appointments. Individuals enrolled need to meet the criterions as: 1) Residents who were registered in the Guangzhou Household Register; 2) Aged 35 years or older; 3) Living in the selected communities for at least 6 months by the day they participant the survey. Residents were excluded when meet criterions as: 1) mental or cognitive disorders including dementia, disturbance of understanding, and deaf-mutters; 2) mobility difficulties including high paraplegia; 3) pregnant or lactating women; 4) malignant tumors under treatment; 5) floating people including those who rented the houses or apartments;6) non-responders during the 3-round mobilization.

This study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association. All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data collection

The residents in the study sites were invited to participate in this study by 3-round mobilization via door-to-door visits or telephone appointments. A structured and interviewer-administered questionnaire was used to survey each participant's demographic information, personal history of disease, living habit, family history and emotional status. Physical examination including measurement of waist circumference, height, weight, blood pressure, heart rate and body fat were performed by standard instruments and protocols. Blood samples were collected and tested according standardized procedure by authorized medical laboratory. Electrocardiograph (ECG) and 24-hour single-lead ECG were recorded in each participant and reports were assessed by two independent cardiologists. Detailed method has been reported in Deng et al's work which was accepted by *Scientific Reports* just now.

Cohort definition

Subjects were diagnosed with NVAF meeting any one criterion as following: 1) ECG screening of subject shows AF pattern; 2) ECG screening does not find AF but subject has AF history with evidence; 3) 24 hours single-lead ECG record shows AF episodes. The criterion of diagnosis of NVAF followed the 2014 AHA/ACC/HRS guideline[6]. ECG and single-lead 24 hours ECG record were performed by well-trained physicians and AF diagnosis were determined by two specific electrophysiological experts. HUA was defined as serum uric acid (SUA) >420μmol/L in males and >360μmol/L in females.The metabolic syndrome (MetS) is defined as having at least three or five characteristic signs as following[7]: Abdominal obesity (defined as waist circumference≥90cm for men and≥80cm for women). Raised Triglycerides level: Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality. Reduced HDL

cholesterol: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality. Raised blood pressure (BP): systolic BP > 130 mmHg or diastolic BP > 85 mmHg or treatment for previously diagnosed HTN. Raised fasting plasma glucose (FPG): FPG > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 DM.

Patient and Public Involvement

The role of patients in this study was residents. They were not involved in the development of the research question and outcome measures. All residents were informed of the right to inquire their data and test results. If residents were diagnosed with cardiovascular disease, they were notified to Guangdong general hospital for further treatment by phone.

Statistical analysis

Numerical variables were expressed as mean±standard deviation and categorical variables were expressed as percentage. Comparison between two groups were made using the Student *t* test or chi-square tests, as appropriate. Multivariate logistic regression models were developed to investigate the risk factors for HUA and the associations between the prevalence of Non-valvular AF and HUA. The odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated to assess the associations. Receiver-operating characteristic (ROC) analyses were used to detect the cutoff value of SUA in prediction of non-valvular AF. SAS software version 9.3 (SAS Institute Inc.; Cary, NC) was used for the statistical analyses. All statistical tests were 2-sided, and a $P<0.05$ was statistically significant.

RESULTS

Baseline characteristics

The study recruited 11488 residents and the incidence of HUA was 39.6% (44.8% in male and 36.7% in female). Among women, the SUA value and the incidence of HUA increased with age. In contrast, the SUA value and incidence of HUA were not affected by age among men [Figure 1]. The incidence of HUA in urban areas is higher than rural areas (Table 1). According to the medical history, the proportion of male with HUA was significantly higher than female. The age was significantly higher in residents with HUA. Regardless of gender, the abdominal circumference and body mass index were significantly greater in residents with HUA. Larger proportion of Non-valvular AF, HTN, DM, Central obesity, Elevated BP, Stroke/Transient Ischemic Attack (TIA) were observed in residents with HUA. According to laboratory examinations, the Hemoglobin (HGB), Platelet (PLT), Red blood cell counts (RBC), Low-density lipoprotein (LDL), Cholesterol (CHOL), fasting plasma glucose (FGP) were significantly higher while Creatinine, High-density lipoprotein were significantly lower in residents with HUA. Significant larger proportion of Reduced HDL cholesterol, Raised TG level and MetS were observed in residents with HUA.

Table1 Baseline characteristics of residents with or without Hyperuricemia

	Total (*n*=11488)	HUA (*n*=4547)	No HUA (*n*=6941)	*P*-value
Clinical characteristics				
Male (n, %)	4047(35.2)	1814(39.9)	2233(32.2)	<0.01
Age (yrs)	58.22±11.74	59.98±11.44	57.06±11.79	<0.01
Urban (n, %)	5403(46.9)	2210(48.6)	3193(46.0)	0.01
Systolic Bp (mmhg)	130.51±20.52	134.16±20.39	128.13±20.25	<0.01

Diastolic Bp (mmhg)	80.70±11.61	82.30±11.60	79.62±11.49	<0.01
Non-valvular AF (n, %)	144(1.3)	91(2.0)	53(0.8)	<0.01
Hypertension (n, %)	3377(29.4)	1744(38.4)	1633(23.5)	<0.01
Diabetes mellitus (n, %)	1050(9.1)	528(11.6)	522(7.5)	<0.01
Elevated BP (n, %) &	6698(58.3)	3092(68.0)	3606(52.0)	<0.01
BMI (kg/m2)	24.01±3.55	25.08±3.55	23.32±3.37	<0.01
Abdominal circumference (cm)	84.41±10.10	87.69±9.61	82.26±9.83	<0.01
Male	84.41±10.11	87.71±9.63	82.26±9.83	<0.01
Female	82.76±9.98	86.36±9.64	80.66±9.56	<0.01
Central obesity (n, %) §	6183(53.8)	2984(65.6)	3199(46.1)	<0.01
Heart failure (n, %)	114(1.0)	50(1.1)	64(0.9)	0.39
Stroke/TIA (n, %)	274(2.4)	128(2.8)	146(2.1)	0.02
Alcohol consumption (n, %)	2467(21.5)	1060(23.3)	1391(20.0)	<0.01
Smoking (n, %)	2451(21.3)	1114(24.5)	1353(19.5)	<0.01
Laboratory examinations				
HGB (g/L)	138.74±14.07	140.14±14.11	137.83±13.97	<0.01
PLT (10^9/L)	243.78±60.67	245.42±61.76	242.71±59.93	0.019
RBC (10^{12}/L)	4.76±0.64	4.80±0.65	4.73±0.63	<0.01
HDL cholesterol(mmol/L)	1.49±0.55	1.36±0.51	1.58±0.56	<0.01
Reduced HDL cholesterol (n, %) □	2589(22.5)	1369(30.1)	1220(17.6)	<0.01
LDL (mmol/L)	3.64±1.03	3.72±1.04	3.58±1.01	<0.01
CHOL (mmol/L)	5.486±1.13	5.57±1.17	5.42±1.11	<0.01
TG (mmol/L)	1.696±1.43	1.47±1.06	2.05±1.18	<0.01
Raised TG level (n, %) £	3787(33.0)	2140(47.1)	1647(23.7)	<0.01
FPG (mmol/L)	5.586±1.57	5.69±1.52	5.51±1.60	<0.01
Elevated FPG (n, %) ¶	3375(29.4)	1653(36.4)	1722(24.8)	<0.01
Uric acid (umol/L)	367.20±98.39	460.60±72.77	306.01±55.62	<0.01
Male	367.00±98.30	460.60±72.70	306.01±55.63	<0.01
Female	340.76±89.40	434.37±64.43	286.30±46.52	<0.01

Creatinine(umol/L)	76.89±25.45	83.78±33.25	72.36±17.22	<0.01
Mets (n, %)	3519(30.6)	2014(44.3)	1505(21.7)	<0.01

BP: Blood pressure; TIA: Transient Ischemic Attack; BMI: Body Mass Index; HGB: Hemoglobin; PLT: Platelet; RBC: Red blood cell counts; FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL: Cholesterol; Mets: Metabolic syndrome

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.

Analysis of prevalence risk of hyperuricemia.

We performed logistic regression analyses to evaluate the risk factors for hyperuricemia (Table 2). After adjusting for possible confounding factors, age (per 10years, OR 1.10, 95% CI 1.06-1.14), living region (urban, OR 1.15, 95% CI 1.06-1.25), alcohol consumption(OR 1.12, 95% CI 1.01-1.24), central obesity(OR 1.82, 95% CI 1.67-1.99), Elevated FPG(OR 1.18, 95% CI 1.08-1.29), Elevated BP(OR 1.34, 95% CI 1.22-1.46), Reduced HDL(OR 1.27, 95% CI 1.15-1.71), Raised Triglycerides level (OR 2.14, 95% CI 1.97-2.35) were strongly associated with the risk of hyperuricemia.

Table2. Analysis of prevalence risk of hyperuricemia in multiple logistic regression model.

Model‡	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	1.10	1.06-1.14	<0.01
Living area(urban)	1.15	1.06-1.25	<0.01
Alcohol consumption	1.12	1.01-1.24	0.03
Central obesity	1.82	1.67-1.99	<0.01
Elevated FPG	1.18	1.08-1.29	<0.01
Elevated BP	1.34	1.22-1.46	<0.01
Reduced HDL	1.27	1.15-1.41	<0.01

Raised Triglycerides level	2.14	1.96-2.35	<0.01

FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL: Cholesterol;

ǂ Adjusted risk factors: age (per 10years), living region, education level, marriage status, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level

Predictive Value of Hyperuricemia on Non-valvular AF.

The adjusted multivariate logistic regression analysis showed that age (per 10 years) (OR 2.31, CI 1.93-2.78), female gender (OR 2.21, CI 1.45-3.36), central obesity (OR 1.93, CI 1.29-2.90,P<0.01), HUA (OR 2.19, 95% CI 1.53-3.12) and history of heart failure (OR 5.13, CI 2.52-10.43) were risk factors for AF prevalence (Table3). ROC curves were generated for the SUA in different gender to determine their diagnostic capability for NVAF. The area under the ROC curve (AUC) for SUA was 0.72 (95% CI: 0.79–0.91) in female and 0.58 (95% CI: 0.51–0.62) in male [Figure 2].

Table3. Increasing odds ratio for non-valvular AF with hyperuricemia.

Variables$^{\omega}$	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	2.31	1.93-2.78	<0.01
Gender(female)	2.21	1.45-3.36	<0.01
Central obesity	1.93	1.29-2.87	<0.01
HUA	2.19	1.53-3.12	<0.01
Heart failure	5.13	2.53-10.43	<0.01

AF: atrial fibrillation; HUA: Hyperuricemia

ω Adjusted risk factors: age (per 10years), gender, heart failure, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level and Hyperuricemia

DISCUSSION

Three main findings can be obtained from this study. Firstly, the prevalence of HUA was 39.6% (44.8% in male and 36.7% in female) and sex related differences were found in residents with HUA; Secondly, the age, living in urban, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL, raised and triglycerides level were strongly associated with risk of HUA; Thirdly, residents with HUA had a markedly increased risk of non-valvular AF, but SUA had moderate predictive value for Non-valvular AF only in female.

The incidence of Hyperuricemia

Regional differences of prevalence of HUA have been reported broadly. According to Liu's review[11], the prevalence of HUA in mainland China from 2000-2014 was 13.3% (19.4% in men and 7.9% in women). Data of some Chinese literatures showed that prevalence in Guangdong province ranged from15 to 20%[11]. The National Health and Nutrition Examination Survey (NHANES) in United States demonstrated that prevalence of HUA was 21.2% in men and 21.6% in women[2]. In other region of Asia like Japan and Taiwan, a similar prevalence as that of the USA was reported[12, 13]. In this study, the prevalence of HUA in Guangzhou area was 39.6% (44.8% in male and 36.7% in female), which was extremely high compared to previous report. The traditional dietary habits of Guangzhou residents might be one of the important reasons. Sex related differences of prevalence of HUA was also observed in our study. The prevalence of HUA increased with age in women while maintained steady high level in men regardless age. A rapidly accelerated prevalence of HUA in women after 55 years old was observed and the prevalence was similar to or even higher than that of men after 65 years old. This situation can be possible explained by greatly decreased estrogen level in postmenopausal

women[14]. Estrogen might promote excretion of SUA due to its effect on the post-secretory tubular reabsorption of SUA, which was confirmed by the effectiveness of hormone replacement therapy in reducing SUA[15, 16].

Risk factors of Hyperuricemia

Due to the increasing incidence of HUA, it is of great clinical significance to search for risk factors for HUA. Risk factors for hyperuricemia might vary among different ethnic groups. In this study, age, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL and Raised Triglycerides level were strongly associated with the risk of HUA. Previous studies showed that hypertriglyceridemia was strongly associated with risk of HUA[17]. The Seychelles Heart Study II revealed the conclusion that high serum TG level was the strongest predictor of HUA[18], our study reached the same conclusion. The mechanism of hypertriglyceridemia leading to HUA might be related to lifestyle[18] or genetic factors[19]. Central obesity, Elevated FPG, Elevated BP, Reduced HDL and Raised Triglycerides level were all the diagnostic component of MetS, it was easy to find that hyperuricemia was closely related to MetS. Yuan's study showed that MetS was 10 times higher in those having SUA ≥10 mg/dL compared to those with SUA <6 mg/dL in adults with normal body mass index[20]. A meta-analysis of more than fifty-four thousand participants showed that elevated SUA was associated with increased risk of MetS[21]. SUA and MetS often accompany each other and promote the occurrence of cardiovascular disease.

Hyperuricemia and Non-valvular Atrial fibrillation

HUA showed a strong relationship with AF in our study. As reported previously, HUA was associated with endothelial dysfunction, oxidative stress, abnormal high levels of inflammatory markers and insulin resistance[22-24]. Result of the Atherosclerosis Risk In Communities (ARIC) study[25] showed that HUA was associated with a greater risk of new onset AF. Unlike our study, the ARIC study enrolled patients aged from 45 to 64 years. Another study from Taiwan[26] showed that serum UA was significantly correlated with left atrial diameter and HUA was a significant risk factor for new-onset AF in the multivariate Cox regression analysis, but patients were defined as HUA only when they suffered from gout attack while asymptomatic patients were not screened out in this study. Differently, we assessed uric acid metabolism status of residents by testing blood uric acid levels in the fasting state. A recent Chinese report also showed that HUA increased AF risk by 2 folds in elderly southwestern residents[27]. Except for the age, only 7.6% AF residents of this study presented with HUA while there was 63.2% of our cohort. Interestingly, the prevalence of HUA was very high in our study, which might be related to eating habits with high intake of overcooked soup and seafood of Guangzhou citizens[28]. Mechanisms underlying the association between urea acid and AF remain unclear but previous report showed that elevated UA was associated with vasoconstriction, vascular smooth muscle cell proliferation, endothelial dysfunction, oxidative stress, local inflammation and insulin resistance[29].

Sex related difference with cardiovascular events has been reported[30]. In Suzuki's and the Atherosclerosis Risk in Communities (ARIC) Study, the result showed that elevated SUA was associated with a higher risk of AF particularly in women. Both SUA and HUA had moderate predictive value of AF in the result of our study. It's worth noting that SUA had higher AUC than

HUA, which means continuous uric acid (UA) level had better predictive value of AF than a cutoff value. As reported previously, the relationship between UA and cardiovascular disease could be observed with normal to high serum level (310-330umol/L) of UA[31-33] and each 1mg/ml increase in UA level was associated with 12% to 20% increase in the risk for cardiovascular and all-cause mortality respectively[34]. Therefore, UA level might have very strong relation with AF. The underlying mechanisms of sex related difference of HUA and AF remains unknow. A study showed that HUA was associated with endothelial dysfunction in post-menopausal women, suggesting that HUA could be an independent risk factor for cardiovascular disease including AF, particularly in postmenopausal women[35].

Limitations

There are two limitations of the study. This study doesn't include resident under age 35, it is unclear whether residents aged less than 35 also have a high incidence of HUA, which requires further research confirmation. Our research is only a cross-Sectional study, the results of this study need to be further clarified through prospective studies and follow-up.

CONCLUSIONS

This large-scale cross-sectional study demonstrates that there is a high prevalence of HUA with sex related difference in Guangzhou residents. Growing age, living in urban, alcohol consumption and component of MetS increase the risk of HUA. Residents with HUA had a markedly increased risk of AF and the uric acid level had moderate predictive value for NVAF only in women.

Contributors

W.L., H.D., Y.X. and S.W. conceived the study, analyzed data, interpreted results and drafted the manuscript. P.G., R.C., F.L., X.F., X.Z., H.L., W.H., Y.L., F.W., M.Z., H.L, J.H. collected data and completed the survey.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship or publication of this article.

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DATA SHARING STATEMENT

The data is available from the corresponding author on reasonable request.

Figure legends

Figure 1. Different prevalence of HUA among male and female in stepwise age categories

HUA, hyperuricemia;

Age categories, every ten years from 35 years old.

Figure 2. Predictive value of HUA or SUA for AF in male and female.

A, receiver operating characteristic (ROC) curve of HUA or SUA for AF in male; B, ROC curve of HUA or SUA for AF in female;

HUA, hyperuricemia; SUA, serum uric acid; A, AUC (area under curve).

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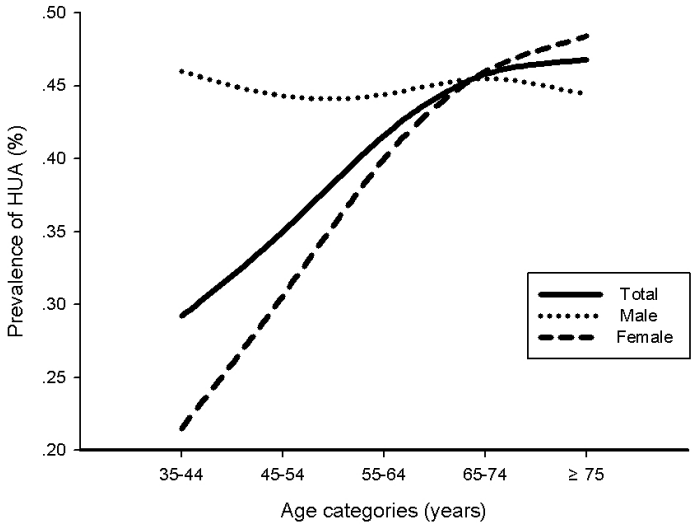
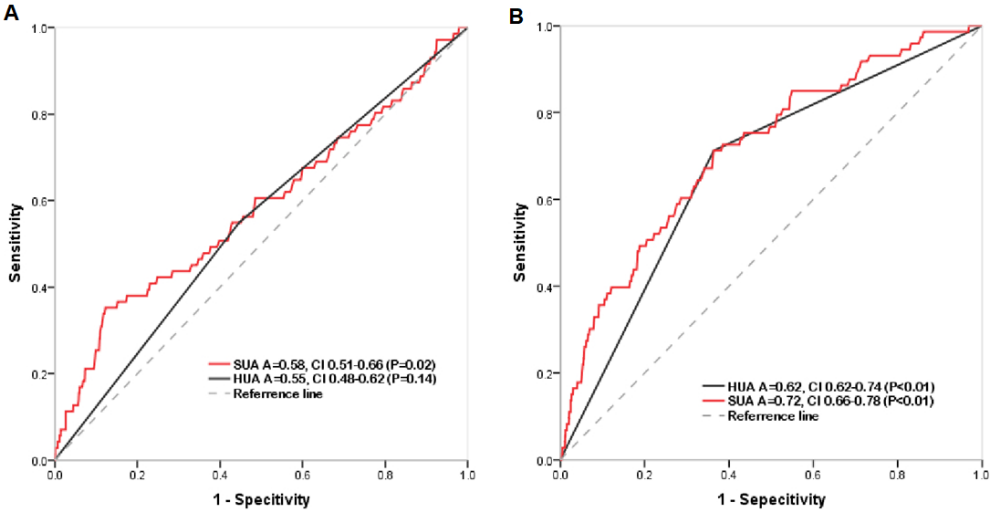


Different prevalence of HUA among male and female in stepwise age categories



A, receiver operating characteristic (ROC) curve of HUA or SUA for AF in male; B, ROC curve of HUA or SUA for AF in female;

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou Heart Study

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High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou Heart Study

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ABSTRACT

Objectives: There are regional variations in hyperuricemia (HUA) epidemiology. The prevalence of HUA and non-valvular atrial fibrillation (NVAF) in southern China is unknown.

Design: A cross-sectional study.

Setting and participants: A total of 11,488 permanent residents aged 35 or older from urban and rural areas of Guangzhou city were enrolled. A questionnaire was used to compile each participant's demographic information and relevant epidemiological factors for HUA and NVAF. All participants were assessed using a panel of blood tests and single-lead 24-hour ECG.

Main outcome measures: HUA was defined as serum uric acid level >420μmol/L in men and >360μmol/L in women. NVAF was diagnosed per 2014 AHA/ACC/HRS guidelines.

Results： The prevalence of HUA was 39.6% (44.8% in men and 36.7% in women), and 144 residents (1.25%) had NVAF. Prevalence of HUA increased with age in women but remained stably high in men. After adjusting for potential confounders, age, living in urban areas, alcohol consumption, central obesity, elevated fasting plasma glucose level, elevated blood pressure, lower HDL cholesterol level and elevated triglycerides level were associated with increased risk of HUA. Residents with HUA were at higher risk for NVAF. Serum uric acid level had a modest predictive value for NVAF in women but not men.

Conclusions: HUA was highly prevalent among citizens of southern China and was a predictor of NVAF among women.

Strengths and limitations of this study:

- This cross-sectional population-based study investigated the prevalence of hyperuricemia and its impact on that of non-valvular atrial fibrillation.
- A large cohort from urban and rural areas of Guangzhou was studied.
- The surveyed areas were all randomized to increase reliability.
- Residents aged under 35 years were not included.
- The results of this cross-sectional study need to be validated in prospective studies.

INTRODUCTION

The prevalence of hyperuricemia (HUA) ranges from 13.3% to 21.6% and varies by sex and among countries or regions [1, 2]. Local differences are apparent within countries, likely influenced by environmental, climatic, economic status and especially dietary habits variations [3, 4]. Although several epidemiological studies reported an association between serum uric acid (SUA) level and cardiovascular conditions such as hypertension, coronary artery disease, vascular dementia, metabolic syndrome, cerebrovascular disease and kidney disease, it was not apparent in others such as the Framingham Heart Study [5].

Atrial fibrillation (AF), the most common clinical cardiac arrhythmia, contributes to increased morbidity and mortality especially in the setting of other cardiovascular risk factors [6]. AF disease burden is estimated to reach 9 million cases by 2050 in China [7], with the increasing prevalence of AF being a global health problem [8, 9]. HUA has been associated with AF [10-13]; however, prevalence of HUA and its potential association with that of non-valvular AF (NVAF) in the typical southern Chinese city of Guangzhou with its particular combination of dietary habits, economic status and climate remain undefined.

The present cross-sectional population-based study aimed to assess the prevalence of HUA and its association with NVAF among Guangzhou residents.

Materials and methods

Study population

We conducted a cardiovascular epidemiological survey (the Guangzhou Heart Study) from July 2015 to August 2017 in Guangzhou. Two streets (Dadong Street and Baiyun Street) were

randomly selected to represent urban areas while one street and two towns (Xiaoguwei Street, Xinzao Town and Nancun Town) were chosen as rural areas. A sample of permanent residents aged 35 or older was selected by cluster sampling in each community of the aforementioned selected areas.

The residents in the study sites were invited to participate in this study by 3-round mobilization via door-to-door visits or telephone appointments. Residents were enrolled if they met all of the following inclusion criteria: 1) registered in the Guangzhou Household Register; 2) aged 35 years or older; and 3) living in the selected communities for at least 6 months by the day they participated in the survey. Residents were excluded if they had any of the following conditions: 1) mental or cognitive disorders including dementia, disturbance of understanding, and deaf-mutters; 2) mobility difficulties including paraplegia; 3) pregnant or lactating women; 4) malignant tumors under treatment; 5) temporary residents including renters; or 6) non-responders during the 3-round mobilization.

This study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association and was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data collection

A structured and interviewer-administered questionnaire was used to survey each participant's demographic information, medical history, social habits, family history and emotional status. Physical examination including measurement of waist circumference, height, weight, blood pressure, heart rate and body fat was performed using standard instruments and protocols. Blood

samples were collected and tested following standardized procedures by an authorized medical laboratory. Electrocardiogram (ECG) and 24-hour single-lead ECG were recorded for each participant and reports were assessed by two independent cardiologists; methodological details were as reported by Deng et al. [14]. A total of 29,196 residents were eligible for inclusion, of whom 12,013 residents participated in the study; the response rate was therefore 41.16%.

Cohort definition

Subjects were diagnosed with NVAF if they met any of the following criteria: 1) AF pattern in ECG screening; 2) No AF in ECG screening but positive AF history; and 3) AF episodes in 24 hours single-lead ECG recording. All residents with atrial fibrillation underwent cardiac ultrasonography to assess for valvular AF. NVAF was diagnosed as per 2014 AHA/ACC/HRS guidelines [6]. ECG and single-lead 24 hours ECG recordings were performed by well-trained physicians, and AF diagnosis was made by two specific electrophysiological experts. HUA was defined as serum uric acid (SUA) level >420μmol/L in men and >360μmol/L in women. The metabolic syndrome (MetS) was defined as having at least three out of the five following characteristic signs [7]: abdominal obesity (defined as waist circumference ≥90cm for men and ≥80cm for women); elevated triglycerides level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality; reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality; elevated blood pressure (BP): systolic BP > 130 mmHg or diastolic BP > 85 mmHg, or treatment for previously diagnosed hypertension; and elevated fasting plasma glucose (FPG): FPG > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

mellitus.

Patient and Public Involvement

The role of patients in this study was residents. They were not involved in the development of the research question and outcome measures. All residents were informed of their right to enquire about their data and test results. If residents were diagnosed with cardiovascular disease, they were notified by phone to present themselves to Guangdong General Hospital for further treatment.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as number (percentage). Comparisons between groups were made using the Student *t* test or chi-square tests, as appropriate. Multivariable logistic regression models were developed to investigate the risk factors for HUA and the associations between the prevalence of NVAF and HUA. Odds ratio (OR) and corresponding 95% confidence interval (95% CI) were calculated to assess the associations. Receiver-operating characteristic (ROC) analyses were used to calculate the predictive value of SUA and HUA for NVAF. SAS software version 9.3 (SAS Institute Inc.; Cary, NC) was used for the statistical analyses. All statistical tests were 2-sided, and a $P<0.05$ was statistically significant.

RESULTS

Baseline characteristics

A total of 12,013 patients were enrolled in the study; 175 patients had atrial fibrillation, which was of valvular origin in 31. A total of 494 patients refused to have a blood test., and therefore 11,488 patients were included in the statistical analysis. The prevalence of HUA was 39.6% (44.8% in men and 36.7% in women, Table 1). Prevalence of HUA increased with age in women but maintained a steady high level in men [Figure 1]. The prevalence of HUA in urban areas was higher than in rural areas (40.9% vs 38.6%, respectively, P=0.003, Figure 2). Based on medical history, the proportion of men with HUA was significantly higher than that of women. Residents with HUA were significantly older. Regardless of gender, abdominal circumference and body mass index were significantly greater in residents with HUA. Larger proportion of NVAF, HTN, DM, central obesity, and stroke/transient ischemic attack (TIA) were observed in residents with HUA. In laboratory testing, hemoglobin (HGB), platelet count (PLT), red blood cell count (RBC), and levels of low-density lipoprotein (LDL), cholesterol (CHOL), and fasting plasma glucose (FGP) were significantly higher while those of creatinine and high-density lipoprotein were significantly lower in residents with HUA. Significant larger proportion of reduced HDL cholesterol, elevated TG level and MetS were observed in residents with HUA.

Table1 Baseline characteristics of residents with or without Hyperuricemia

	Total (*n*=11488)	HUA (*n*=4547)	No HUA (*n*=6941)	*P*-value
Clinical characteristics				
Male (n, %)	4047(35.2)	1814(39.9)	2233(32.2)	<0.01
Age (yrs)	58.22±11.74	59.98±11.44	57.06±11.79	<0.01
Urban (n, %)	5403(46.9)	2210(48.6)	3193(46.0)	0.01
Systolic Bp (mmhg)	130.51±20.52	134.16±20.39	128.13±20.25	<0.01

Diastolic Bp (mmhg)	80.70±11.61	82.30±11.60	79.62±11.49	<0.01
Non-valvular AF (n, %)	144(1.3)	91(2.0)	53(0.8)	<0.01
Hypertension (n, %)	3377(29.4)	1744(38.4)	1633(23.5)	<0.01
Diabetes mellitus (n, %)	1050(9.1)	528(11.6)	522(7.5)	<0.01
Elevated BP (n, %) &	6698(58.3)	3092(68.0)	3606(52.0)	<0.01
BMI (kg/m^2)	24.01±3.55	25.08±3.55	23.32±3.37	<0.01
Abdominal circumference (cm)	84.41±10.10	87.69±9.61	82.26±9.83	<0.01
Male	84.41±10.11	87.71±9.63	82.26±9.83	<0.01
Female	82.76±9.98	86.36±9.64	80.66±9.56	<0.01
Central obesity (n, %) §	6183(53.8)	2984(65.6)	3199(46.1)	<0.01
Heart failure (n, %)	114(1.0)	50(1.1)	64(0.9)	0.39
Stroke/TIA (n, %)	274(2.4)	128(2.8)	146(2.1)	0.02
Alcohol consumption (n, %)	2467(21.5)	1060(23.3)	1391(20.0)	<0.01
Smoking (n, %)	2451(21.3)	1114(24.5)	1353(19.5)	<0.01
Laboratory examinations				
HGB (g/L)	138.74±14.07	140.14±14.11	137.83±13.97	<0.01
PLT (10^9/L)	243.78±60.67	245.42±61.76	242.71±59.93	0.019
RBC (10^{12}/L)	4.76±0.64	4.80±0.65	4.73±0.63	<0.01
HDL cholesterol(mmol/L)	1.49±0.55	1.36±0.51	1.58±0.56	<0.01
Reduced HDL cholesterol (n, %) □	2589(22.5)	1369(30.1)	1220(17.6)	<0.01
LDL (mmol/L)	3.64±1.03	3.72±1.04	3.58±1.01	<0.01
CHOL (mmol/L)	5.486±1.13	5.57±1.17	5.42±1.11	<0.01
TG (mmol/L)	1.696±1.43	1.47±1.06	2.05±1.18	<0.01
Raised TG level (n, %) £	3787(33.0)	2140(47.1)	1647(23.7)	<0.01
FPG (mmol/L)	5.586±1.57	5.69±1.52	5.51±1.60	<0.01
Elevated FPG (n, %) ¶	3375(29.4)	1653(36.4)	1722(24.8)	<0.01
Uric acid (umol/L)	367.20±98.39	460.60±72.77	306.01±55.62	<0.01
Male	367.00±98.30	460.60±72.70	306.01±55.63	<0.01
Female	340.76±89.40	434.37±64.43	286.30±46.52	<0.01

Creatinine(umol/L)	76.89±25.45	83.78±33.25	72.36±17.22	<0.01

BP: Blood pressure; TIA: Transient Ischemic Attack; BMI: Body Mass Index; HGB: Hemoglobin; PLT: Platelet; RBC: Red blood cell counts; FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL: Cholesterol; Mets: Metabolic syndrome

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.

Analysis of prevalence risk of hyperuricemia.

We performed logistic regression analyses to evaluate the risk factors for hyperuricemia (Table 2). After adjusting for possible confounders, age (per 10years, OR 1.10, 95% CI 1.06-1.14), living region (urban, OR 1.15, 95% CI 1.06-1.25), alcohol consumption (OR 1.12, 95% CI 1.01-1.24), central obesity (OR 1.82, 95% CI 1.67-1.99), elevated FPG (OR 1.18, 95% CI 1.08-1.29), elevated BP (OR 1.34, 95% CI 1.22-1.46), reduced HDL (OR 1.27, 95% CI 1.15-1.71), and elevated triglycerides level (OR 2.14, 95% CI 1.97-2.35) were strongly associated with risk for hyperuricemia.

Table2. Analysis of prevalence risk of hyperuricemia in multiple logistic regression model.

Model‡	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	1.10	1.06-1.14	<0.01
Living area(urban)	1.15	1.06-1.25	<0.01
Alcohol consumption	1.12	1.01-1.24	0.03
Central obesity §	1.82	1.67-1.99	<0.01
Elevated FPG ¶	1.18	1.08-1.29	<0.01
Elevated BP &	1.34	1.22-1.46	<0.01

Reduced HDL □	1.27	1.15-1.41	<0.01
Raised Triglycerides level £	2.14	1.96-2.35	<0.01

FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL: Cholesterol;

ǂ Adjusted risk factors: age (per 10years), living region, education level, marriage status, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.

Predictive value of hyperuricemia on non-valvular AF.

The adjusted multivariable logistic regression analysis showed that age (per 10 years) (OR 2.31, CI 1.93-2.78), female gender (OR 2.21, CI 1.45-3.36), central obesity (OR 1.93, CI 1.29-2.90,P<0.01), HUA (OR 2.19, 95% CI 1.53-3.12) and history of heart failure (OR 5.13, CI 2.52-10.43) were risk factors for AF prevalence (Table 3). ROC curves were generated for SUA by gender to determine its diagnostic capability for NVAF. The area under the ROC curve (AUC) for SUA was 0.72 (95% CI: 0.79–0.91) in women and 0.58 (95% CI: 0.51–0.62) in men [Figure 3].

Table3. Increasing odds ratio for non-valvular AF with hyperuricemia.

Variables[ω]	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	2.31	1.93-2.78	<0.01

Gender(female)	2.21	1.45-3.36	<0.01
Central obesity	1.93	1.29-2.87	<0.01
HUA	2.19	1.53-3.12	<0.01
Heart failure	5.13	2.53-10.43	<0.01

AF: atrial fibrillation; HUA: Hyperuricemia

ω Adjusted risk factors: age (per 10years), gender, heart failure, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level and Hyperuricemia

DISCUSSION

The present study had three main findings. Firstly, the prevalence of HUA was 39.6% (44.8% in men and 36.7% in women) with sex related differences in residents with HUA. Secondly, the age, living in urban, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL, and elevated triglycerides level were strongly associated with risk of HUA. Thirdly, residents with HUA had a markedly increased risk of NVAF, and SUA had moderate predictive value for NVAF only in women.

The prevalence of hyperuricemia

Regional differences in prevalence of HUA have been reported. According to Liu's review [15], the prevalence of HUA in mainland China from 2000-2014 was 13.3% (19.4% in men and 7.9% in women). In Chinese publications, prevalence of HUA in Guangdong province ranged from 15 to 20% [15]. The National Health and Nutrition Examination Survey (NHANES) in the United States documented a 21.2% HUA prevalence in men and 21.6% in women [2] which was similar to that in Japan and Taiwan [16, 17]. In this study, the prevalence of HUA in Guangzhou area was 39.6% (44.8% in men and 36.7% in women), which was considerably higher than that in

previous reports. The traditional dietary habits of Guangzhou residents might be one of the important reasons. Sex related differences in HUA prevalence also were observed in our study. The prevalence of HUA increased with age in women while remaining at a steady high level in men regardless of age. A rapidly increasing prevalence of HUA in women older than 55 years old was observed; the prevalence was similar to or even higher than that of men after 65 years old. The latter finding might reflect greatly decreased estrogen level in postmenopausal women [18]. Estrogen might promote excretion of SUA via its effect on post-secretory tubular reabsorption of SUA, as confirmed by the effectiveness of hormone replacement therapy in reducing SUA [19, 20].

Risk factors of hyperuricemia

Due to the increasing prevalence of HUA, it is of great clinical significance to search for its risk factors. Risk factors for hyperuricemia might vary among ethnic groups. In this study, age, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL and elevated triglycerides level were strongly associated with the risk of HUA. Previous studies showed that hypertriglyceridemia was strongly associated with risk of HUA [21]. Consistent with our study, the Seychelles Heart Study II documented that high serum TG level was the strongest predictor of HUA [22]. The mechanism of hypertriglyceridemia leading to HUA might be related to lifestyle [22] or genetic factors [23]. Central obesity, elevated FPG, elevated BP, reduced HDL and elevated triglycerides level are all diagnostic components of MetS; therefore, hyperuricemia was closely related to MetS. Yuan's study showed that MetS was 10 times higher in individuals with SUA ≥10 mg/dL than in adults with SUA <6 mg/dL and normal body mass index [24]. A meta-analysis of more than fifty-four thousand participants showed that elevated SUA was associated with

increased risk of MetS [25]. SUA and MetS often accompany each other and promote the occurrence of cardiovascular disease.

Hyperuricemia and non-valvular atrial fibrillation

HUA showed a strong relationship with AF in our study. As reported previously, HUA was associated with endothelial dysfunction, oxidative stress, abnormal high levels of inflammatory markers and insulin resistance [26-28]. In the Atherosclerosis Risk In Communities (ARIC) study [29], HUA was associated with a greater risk of new onset AF. In contrast to our study, the ARIC study enrolled patients aged 45 to 64 years. Another study from Taiwan [30] showed that SUA significantly correlated with left atrial diameter and that HUA was a significant risk factor for new-onset AF in multivariable Cox regression analysis; however, HUA was diagnosed only when individuals suffered from a gout attack, while in the present study asymptomatic patients were not excluded and uric acid metabolism status of residents was assessed by measuring blood uric acid levels in the fasting state. A recent Chinese report also showed that HUA increased AF risk by 2-fold among elderly southwestern residents [31]. Only 7.6% AF residents in the latter study presented with HUA while 63.2% did not so in the present study cohort. Mechanisms underlying the association between uric acid level and AF remain unclear; however, elevated UA has been associated with vasoconstriction, vascular smooth muscle cell proliferation, endothelial dysfunction, oxidative stress, local inflammation and insulin resistance[32].

Differences in cardiovascular events rates by gender have been reported[33]. In the study by Suzuki and the Atherosclerosis Risk in Communities (ARIC) Study, elevated SUA was associated with a higher risk of AF particularly in women. Both SUA and HUA had moderate

predictive value for AF in the present study. It is worth noting that SUA had higher AUC than HUA, which indicates a better predictive value for AF for continuous rather than a cutoff for uric acid (UA). As reported previously, the relationship between UA and cardiovascular disease is apparent with normal to high UA serum level (310-330umol/L) [34-36]; each 1mg/ml increase in UA level was associated with 12% to 20% increase in the risk for cardiovascular and all-cause mortality, respectively [37]. Therefore, UA level might be strongly associated with AF. The bases for sex related differences in HUA and AF remain unknow. HUA has been associated with endothelial dysfunction in post-menopausal women, suggesting that HUA could be an independent risk factor for cardiovascular disease including AF, particularly among postmenopausal women [38].

Limitations

The present study is limited by its cross-sectional design, warranting prospective studies with appropriate follow-up to validate findings; and lack of inclusion of residents aged under 35 years whose HUA prevalence remains unknown.

CONCLUSIONS

This large-scale cross-sectional study demonstrated a high prevalence of HUA with sex related differences among Guangzhou residents. Increasing age, living in an urban setting, alcohol consumption and components of MetS increase the risk of HUA. Residents with HUA had a markedly increased risk for AF and the uric acid level had moderate predictive value for NVAF only in women.

Contributors

W.L., H.D., Y.X. and S.W. conceived the study, analyzed data, interpreted results and drafted the manuscript. P.G., R.C., F.L., X.F., X.Z., H.L., W.H., Y.L., F.W., M.Z., H.L, J.H., W.W. collected data and completed the survey.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship or publication of this article.

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DATA SHARING STATEMENT

The data are available from the corresponding author upon reasonable request.

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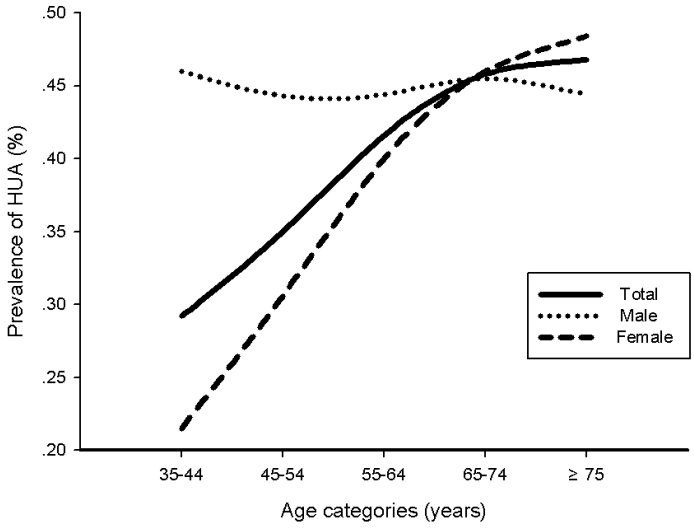
Figure legends

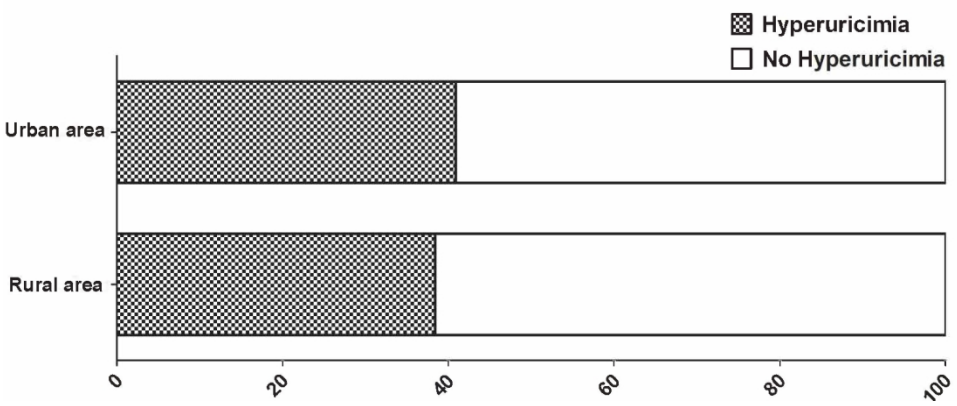
Figure 1. Differential prevalence of hyperuricemia (HUA) among men and women across 10-year age intervals starting at 35.

Figure 2. Prevalence of hyperuricemia in urban and rural areas.

Figure 3. Receiver operating characteristic (ROC) curves for determination of predictive value of hyperuricemia (HUA) or serum uric acid (SUA) for AF in men (A) and women (B). AUC (area under curve).



Different prevalence of HUA among male and female in stepwise age categories



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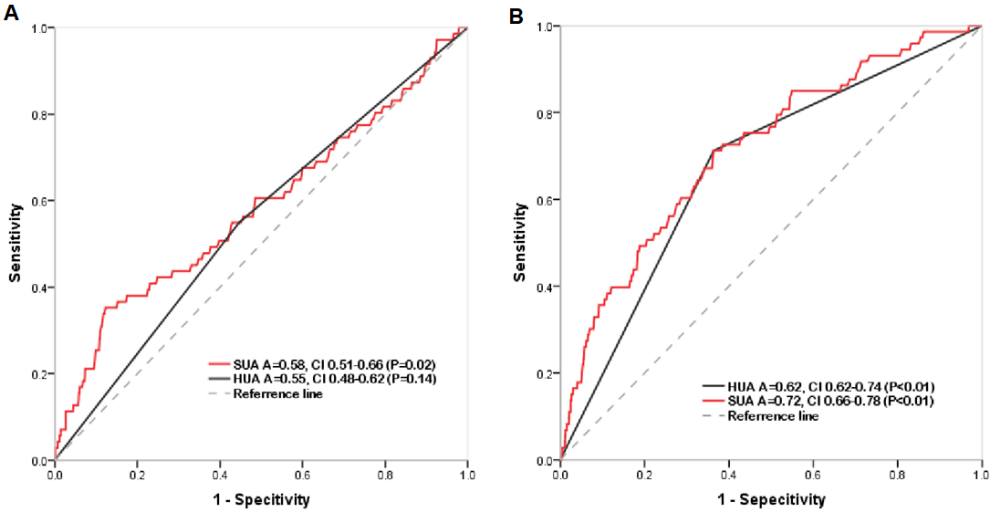

A, receiver operating characteristic (ROC) curve of HUA or SUA for AF in male; B, ROC curve of HUA or SUA for AF in female;

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract L48
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found L49-L63
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported L90-L100
Objectives	3	State specific objectives, including any prespecified hypotheses L101-L105
Methods		
Study design	4	Present key elements of study design early in the paper L109-L114
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection L115-137
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants L117-L123
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable L139-L155
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group L164-L173
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at L109-L114, L136-L137
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding L165-L166
		(*b*) Describe any methods used to examine subgroups and interactions L166-L171
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed L136-L137, L177-L179
		(b) Give reasons for non-participation at each stage L177-L179
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders L179-L191
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures L179-191
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included L206-L212, L228-L234
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives L242-L247
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias L312-L314
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence L249-L309
Generalisability	21	Discuss the generalisability (external validity) of the study results L317-L321
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based L336-L339

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou Heart Study

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Primary Subject Heading:	Epidemiology

Secondary Subject Heading:	Public health
Keywords:	Cardiac Epidemiology < CARDIOLOGY, EPIDEMIOLOGY, CARDIOLOGY

High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou Heart Study

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ABSTRACT

Objectives: There are country and regional variations in the prevalence of hyperuricemia (HUA). The prevalence of HUA and non-valvular atrial fibrillation (NVAF) in southern China is unknown.

Design: A cross-sectional study.

Setting and participants: A total of 11,488 permanent residents aged 35 or older from urban and rural areas of Guangzhou city were enrolled. A questionnaire was used to compile each participant's demographic information and relevant epidemiological factors for HUA and NVAF. All participants were assessed using a panel of blood tests and single-lead 24-hour electrocardiogram.

Main outcome measures: HUA was defined as serum uric acid level >420μmol/L in men and >360μmol/L in women. NVAF was diagnosed per guidelines.

Results： The prevalence of HUA was 39.6% (44.8% in men and 36.7% in women), and 144 residents (1.25%) had NVAF. Prevalence of HUA increased with age in women but remained stably high in men. After adjusting for potential confounders, age, living in urban areas, alcohol consumption, central obesity, elevated fasting plasma glucose level, elevated blood pressure, lower high-density lipoprotein cholesterol level and elevated triglycerides level were associated with increased risk of HUA. Residents with HUA were at higher risk for NVAF. Serum uric acid level had a modest predictive value for NVAF in women but not men.

Conclusions: HUA was highly prevalent among citizens of southern China and was a predictor of NVAF among women.

Strengths and limitations of this study:

- This cross-sectional population-based study investigated the prevalence of hyperuricemia and its impact on that of non-valvular atrial fibrillation.
- A large cohort from urban and rural areas of Guangzhou was studied.
- The surveyed areas were all randomized to increase reliability.
- Residents aged under 35 years were not included.
- The results of this cross-sectional study need to be validated in prospective studies.

INTRODUCTION

The prevalence of hyperuricemia (HUA) ranges from 13.3% to 21.6% and varies by sex and among countries or regions [1, 2]. Local differences are apparent within countries, likely influenced by environmental, climatic, economic status and especially dietary habits variations [3, 4]. Although several epidemiological studies reported an association between serum uric acid (SUA) level and cardiovascular conditions such as hypertension, coronary artery disease, vascular dementia, metabolic syndrome, cerebrovascular disease and kidney disease, it was not apparent in others such as the Framingham Heart Study [5].

Atrial fibrillation (AF), the most common clinical cardiac arrhythmia, contributes to increased morbidity and mortality especially in the setting of other cardiovascular risk factors [6]. AF disease burden is estimated to reach 9 million cases by 2050 in China [7], with the increasing prevalence of AF being a global health problem [8, 9]. HUA has been associated with AF [10-13]; however, prevalence of HUA and its potential association with that of non-valvular AF (NVAF) in the typical southern Chinese city of Guangzhou with its particular combination of dietary habits, economic status and climate remain undefined.

The present cross-sectional population-based study aimed to assess the prevalence of HUA and its association with NVAF among Guangzhou residents.

Materials and methods

Study population

We conducted a cardiovascular epidemiological survey (the Guangzhou Heart Study) from July 2015 to August 2017 in Guangzhou. Two streets (Dadong Street and Baiyun Street) were

randomly selected to represent urban areas while one street and two towns (Xiaoguwei Street, Xinzao Town and Nancun Town) were chosen as rural areas. A sample of permanent residents aged 35 or older was selected by cluster sampling in each community of the aforementioned selected areas.

The residents in the study sites were invited to participate in this study by 3-round mobilization via door-to-door visits or telephone appointments. Residents were enrolled if they met all of the following inclusion criteria: 1) registered in the Guangzhou Household Register; 2) aged 35 years or older; and 3) living in the selected communities for at least 6 months by the day they participated in the survey. Residents were excluded if they had any of the following conditions: 1) mental or cognitive disorders including dementia, disturbance of understanding, and deaf-mutters; 2) mobility difficulties including paraplegia; 3) pregnant or lactating women; 4) malignant tumors under treatment; 5) temporary residents including renters; or 6) non-responders during the 3-round mobilization.

This study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association and was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All residents needed to sign an informed consent prior to the initiation of the study.

Data collection

A structured and interviewer-administered questionnaire was used to survey each participant's demographic information, medical history, social habits, family history and emotional status. Physical examination including measurement of waist circumference, height, weight, blood

pressure, heart rate and body fat was performed using standard instruments and protocols. Blood samples were collected and tested following standardized procedures by an authorized medical laboratory. Electrocardiogram (ECG) and 24-hour single-lead ECG were recorded for each participant and reports were assessed by two independent cardiologists; methodological details were as reported by Deng et al. [14]. A total of 29,196 residents were eligible for inclusion, of whom 12,013 residents participated in the study; the response rate was therefore 41.16%.

Cohort definition

Subjects were diagnosed with NVAF if they met any of the following criteria: 1) AF pattern in ECG screening; 2) No AF in ECG screening but positive AF history; and 3) AF episodes in 24 hours single-lead ECG recording. All residents with atrial fibrillation underwent cardiac ultrasonography to assess for valvular AF. NVAF was diagnosed as per guidelines [6]. ECG and single-lead 24 hours ECG recordings were performed by well-trained physicians, and AF diagnosis was made by two specific electrophysiological experts. HUA was defined as serum uric acid (SUA) level >420μmol/L in men and >360μmol/L in women. The metabolic syndrome (MetS) was defined as having at least three out of the five following characteristic signs [7]: abdominal obesity (defined as waist circumference ≥90cm for men and ≥80cm for women); elevated triglycerides level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality; reduced high-density lipoprotein (HDL) cholesterol: < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality; elevated blood pressure (BP): systolic BP > 130 mmHg or diastolic BP > 85 mmHg, or treatment for previously diagnosed hypertension; and elevated fasting plasma glucose (FPG): FPG > 100

mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes mellitus.

Patient and Public Involvement

Residents were not involved in the development of the research question and outcome measures. All residents were informed of their right to enquire about their data and test results. If residents were diagnosed with cardiovascular disease, they were notified by phone to present themselves to Guangdong General Hospital for further treatment.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as number (percentage). Comparisons between groups were made using the Student *t* test or chi-square tests, as appropriate. Multivariable logistic regression models were developed to investigate the risk factors for HUA and the associations between the prevalence of NVAF and HUA. Odds ratio (OR) and corresponding 95% confidence interval (95% CI) were calculated to assess the associations. Receiver-operating characteristic (ROC) analyses were used to calculate the predictive value of SUA and HUA for NVAF. SAS software version 9.3 (SAS Institute Inc.; Cary, NC) was used for the statistical analyses. All statistical tests were 2-sided, and a $P<0.05$ was statistically significant.

RESULTS

Baseline characteristics

A total of 12,013 patients were enrolled in the study; 175 patients had atrial fibrillation, which

was of valvular origin in 31. A total of 494 patients refused to have a blood test., and therefore 11,488 patients were included in the statistical analysis. The prevalence of HUA was 39.6% (44.8% in men and 36.7% in women, Table 1). Prevalence of HUA increased with age in women but maintained a steady high level in men [Figure 1]. The prevalence of HUA in urban areas was higher than in rural areas (40.9% vs 38.6%, respectively, P=0.003, Figure 2). Based on medical history, the proportion of men with HUA was significantly higher than that of women. Residents with HUA were significantly older. Regardless of gender, abdominal circumference and body mass index were significantly greater in residents with HUA. A higher proportion of NVAF, HTN, DM, central obesity, and stroke/transient ischemic attack (TIA) were observed in residents with HUA. In laboratory testing, hemoglobin (HGB), platelet count (PLT), red blood cell count (RBC), and levels of low-density lipoprotein (LDL), cholesterol (CHOL), and fasting plasma glucose (FGP) were significantly higher while those of creatinine and high-density lipoprotein were significantly lower in residents with HUA. Significant larger proportion of reduced HDL cholesterol, elevated TG level and MetS were observed in residents with HUA.

Table1 Baseline characteristics of residents with or without Hyperuricemia

	Total (*n*=11488)	HUA (*n*=4547)	No HUA (*n*=6941)	*P*-value
Clinical characteristics				
Male (n, %)	4047(35.2)	1814(39.9)	2233(32.2)	<0.01
Age (yrs)	58.22±11.74	59.98±11.44	57.06±11.79	<0.01
Urban (n, %)	5403(46.9)	2210(48.6)	3193(46.0)	0.01
Systolic Bp (mmhg)	130.51±20.52	134.16±20.39	128.13±20.25	<0.01
Diastolic Bp (mmhg)	80.70±11.61	82.30±11.60	79.62±11.49	<0.01
Non-valvular AF (n, %)	144(1.3)	91(2.0)	53(0.8)	<0.01

Hypertension (n, %)	3377(29.4)	1744(38.4)	1633(23.5)	<0.01
Diabetes mellitus (n, %)	1050(9.1)	528(11.6)	522(7.5)	<0.01
Elevated BP (n, %) &	6698(58.3)	3092(68.0)	3606(52.0)	<0.01
BMI (kg/m^2)	24.01±3.55	25.08±3.55	23.32±3.37	<0.01
Abdominal circumference (cm)	84.41±10.10	87.69±9.61	82.26±9.83	<0.01
Male	84.41±10.11	87.71±9.63	82.26±9.83	<0.01
Female	82.76±9.98	86.36±9.64	80.66±9.56	<0.01
Central obesity (n, %) §	6183(53.8)	2984(65.6)	3199(46.1)	<0.01
Heart failure (n, %)	114(1.0)	50(1.1)	64(0.9)	0.39
Stroke/TIA (n, %)	274(2.4)	128(2.8)	146(2.1)	0.02
Alcohol consumption (n, %)	2467(21.5)	1060(23.3)	1391(20.0)	<0.01
Smoking (n, %)	2451(21.3)	1114(24.5)	1353(19.5)	<0.01
Laboratory examinations				
HGB (g/L)	138.74±14.07	140.14±14.11	137.83±13.97	<0.01
PLT (10^9/L)	243.78±60.67	245.42±61.76	242.71±59.93	0.019
RBC (10^{12}/L)	4.76±0.64	4.80±0.65	4.73±0.63	<0.01
HDL cholesterol(mmol/L)	1.49±0.55	1.36±0.51	1.58±0.56	<0.01
Reduced HDL cholesterol (n, %) □	2589(22.5)	1369(30.1)	1220(17.6)	<0.01
LDL (mmol/L)	3.64±1.03	3.72±1.04	3.58±1.01	<0.01
CHOL (mmol/L)	5.486±1.13	5.57±1.17	5.42±1.11	<0.01
TG (mmol/L)	1.696±1.43	1.47±1.06	2.05±1.18	<0.01
Raised TG level (n, %) £	3787(33.0)	2140(47.1)	1647(23.7)	<0.01
FPG (mmol/L)	5.586±1.57	5.69±1.52	5.51±1.60	<0.01
Elevated FPG (n, %) ¶	3375(29.4)	1653(36.4)	1722(24.8)	<0.01
Uric acid (umol/L)	367.20±98.39	460.60±72.77	306.01±55.62	<0.01
Male	367.00±98.30	460.60±72.70	306.01±55.63	<0.01
Female	340.76±89.40	434.37±64.43	286.30±46.52	<0.01
Creatinine(umol/L)	76.89±25.45	83.78±33.25	72.36±17.22	<0.01

193 BP: Blood pressure; TIA: Transient Ischemic Attack; BMI: Body Mass Index; HGB: Hemoglobin; PLT: Platelet; RBC: Red
194 blood cell counts; FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein;

CHOL: Cholesterol; Mets: Metabolic syndrome

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.

Analysis of prevalence risk of hyperuricemia.

We performed logistic regression analyses to evaluate the risk factors for hyperuricemia (Table 2). After adjusting for possible confounders, age (per 10years, OR 1.10, 95% CI 1.06-1.14), living region (urban, OR 1.15, 95% CI 1.06-1.25), alcohol consumption (OR 1.12, 95% CI 1.01-1.24), central obesity (OR 1.82, 95% CI 1.67-1.99), elevated FPG (OR 1.18, 95% CI 1.08-1.29), elevated BP (OR 1.34, 95% CI 1.22-1.46), reduced HDL (OR 1.27, 95% CI 1.15-1.71), and elevated triglycerides level (OR 2.14, 95% CI 1.97-2.35) were strongly associated with risk for hyperuricemia.

Table2. Analysis of prevalence risk of hyperuricemia in multiple logistic regression model.

Model♯	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	1.10	1.06-1.14	<0.01
Living area(urban)	1.15	1.06-1.25	<0.01
Alcohol consumption	1.12	1.01-1.24	0.03
Central obesity §	1.82	1.67-1.99	<0.01
Elevated FPG ¶	1.18	1.08-1.29	<0.01
Elevated BP &	1.34	1.22-1.46	<0.01
Reduced HDL □	1.27	1.15-1.41	<0.01
Raised Triglycerides level £	2.14	1.96-2.35	<0.01

FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL:

Cholesterol;

ǂ Adjusted risk factors: age (per 10years), living region, education level, marriage status, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.

Predictive value of hyperuricemia on non-valvular AF.

The adjusted multivariable logistic regression analysis showed that age (per 10 years) (OR 2.31, CI 1.93-2.78), female gender (OR 2.21, CI 1.45-3.36), central obesity (OR 1.93, CI 1.29-2.90,P<0.01), HUA (OR 2.19, 95% CI 1.53-3.12) and history of heart failure (OR 5.13, CI 2.52-10.43) were risk factors for AF prevalence (Table 3). ROC curves were generated for SUA by gender to determine its diagnostic capability for NVAF. The area under the ROC curve (AUC) for SUA was 0.72 (95% CI: 0.79–0.91) in women and 0.58 (95% CI: 0.51–0.62) in men [Figure 3].

Table3. Increasing odds ratio for non-valvular AF with hyperuricemia.

Variables[ω]	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	2.31	1.93-2.78	<0.01
Gender(female)	2.21	1.45-3.36	<0.01
Central obesity	1.93	1.29-2.87	<0.01
HUA	2.19	1.53-3.12	<0.01

Heart failure	5.13	2.53-10.43	<0.01

AF: atrial fibrillation; HUA: Hyperuricemia

ω Adjusted risk factors: age (per 10years), gender, heart failure, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level and Hyperuricemia

DISCUSSION

The present study had three main findings. Firstly, the prevalence of HUA was 39.6% (44.8% in men and 36.7% in women) with sex related differences in residents with HUA. Secondly, the age, living in urban, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL, and elevated triglycerides level were strongly associated with risk of HUA. Thirdly, residents with HUA had a markedly increased risk of NVAF, and SUA had moderate predictive value for NVAF only in women.

The prevalence of hyperuricemia

Regional differences in prevalence of HUA have been reported. According to Liu's review [15], the prevalence of HUA in mainland China from 2000-2014 was 13.3% (19.4% in men and 7.9% in women). In Chinese publications, prevalence of HUA in Guangdong province ranged from 15 to 20% [15]. The National Health and Nutrition Examination Survey (NHANES) in the United States documented a 21.2% HUA prevalence in men and 21.6% in women [2] which was similar to that in Japan and Taiwan [16, 17]. In this study, the prevalence of HUA in Guangzhou area was 39.6% (44.8% in men and 36.7% in women), which was considerably higher than that in previous reports. The traditional dietary habits of Guangzhou residents might be one of the important reasons. Sex related differences in HUA prevalence also were observed in our study.

The prevalence of HUA increased with age in women while remaining at a steady high level in men regardless of age. A rapidly increasing prevalence of HUA in women older than 55 years old was observed; the prevalence was similar to or even higher than that of men after 65 years old. The latter finding might reflect greatly decreased estrogen level in postmenopausal women [18]. Estrogen might promote excretion of SUA via its effect on post-secretory tubular reabsorption of SUA, as confirmed by the effectiveness of hormone replacement therapy in reducing SUA [19, 20].

Risk factors of hyperuricemia

Due to the increasing prevalence of HUA, it is of great clinical significance to search for its risk factors. Risk factors for hyperuricemia might vary among ethnic groups. In this study, age, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL and elevated triglycerides level were strongly associated with the risk of HUA. Previous studies showed that hypertriglyceridemia was strongly associated with risk of HUA [21]. Consistent with our study, the Seychelles Heart Study II documented that high serum TG level was the strongest predictor of HUA [22]. The mechanism of hypertriglyceridemia leading to HUA might be related to lifestyle [22] or genetic factors [23]. Central obesity, elevated FPG, elevated BP, reduced HDL and elevated triglycerides level are all diagnostic components of MetS; therefore, hyperuricemia was closely related to MetS. Yuan's study showed that MetS was 10 times higher in individuals with SUA ≥10 mg/dL than in adults with SUA <6 mg/dL and normal body mass index [24]. A meta-analysis of more than fifty-four thousand participants showed that elevated SUA was associated with increased risk of MetS [25]. SUA and MetS often accompany each other and promote the occurrence of cardiovascular disease.

Hyperuricemia and non-valvular atrial fibrillation

HUA showed a strong relationship with AF in our study. As reported previously, HUA was associated with endothelial dysfunction, oxidative stress, abnormal high levels of inflammatory markers and insulin resistance [26-28]. In the Atherosclerosis Risk In Communities (ARIC) study [29], HUA was associated with a greater risk of new onset AF. In contrast to our study, the ARIC study enrolled patients aged 45 to 64 years. Another study from Taiwan [30] showed that SUA significantly correlated with left atrial diameter and that HUA was a significant risk factor for new-onset AF in multivariable Cox regression analysis; however, HUA was diagnosed only when individuals suffered from a gout attack, while in the present study asymptomatic patients were not excluded and uric acid metabolism status of residents was assessed by measuring blood uric acid levels in the fasting state. A recent Chinese report also showed that HUA increased AF risk by 2-fold among elderly southwestern residents [31]. Only 7.6% AF residents in the latter study presented with HUA while 63.2% did not so in the present study cohort. Mechanisms underlying the association between uric acid level and AF remain unclear; however, elevated UA has been associated with vasoconstriction, vascular smooth muscle cell proliferation, endothelial dysfunction, oxidative stress, local inflammation and insulin resistance[32].

Differences in cardiovascular events rates by gender have been reported[33]. In the study by Suzuki and the Atherosclerosis Risk in Communities (ARIC) Study, elevated SUA was associated with a higher risk of AF particularly in women. Both SUA and HUA had moderate predictive value for AF in the present study. It is worth noting that SUA had higher AUC than HUA, which indicates a better predictive value for AF for continuous rather than a cutoff for uric

acid (UA). As reported previously, the relationship between UA and cardiovascular disease is apparent with normal to high UA serum level (310-330umol/L) [34-36]; each 1mg/ml increase in UA level was associated with 12% to 20% increase in the risk for cardiovascular and all-cause mortality, respectively [37]. Therefore, UA level might be strongly associated with AF. The bases for sex related differences in HUA and AF remain unknow. HUA has been associated with endothelial dysfunction in post-menopausal women, suggesting that HUA could be an independent risk factor for cardiovascular disease including AF, particularly among postmenopausal women [38].

Limitations

The present study is limited by its cross-sectional design, warranting prospective studies with appropriate follow-up to validate findings; and lack of inclusion of residents aged under 35 years whose HUA prevalence remains unknown.

CONCLUSIONS

This large-scale cross-sectional study demonstrated a high prevalence of HUA with sex related differences among Guangzhou residents. Increasing age, living in an urban setting, alcohol consumption and components of MetS increase the risk of HUA. Residents with HUA had a markedly increased risk for AF and the uric acid level had moderate predictive value for NVAF only in women.

Contributors

W.L., H.D., Y.X. and S.W. conceived the study, analyzed data, interpreted results and drafted the manuscript. P.G., R.C., F.L., X.F., X.Z., H.L., W.H., Y.L., F.W., M.Z., H.L, J.H., W.W. collected data and completed the survey.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship or publication of this article.

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DATA SHARING STATEMENT

The data are available from the corresponding author upon reasonable request.

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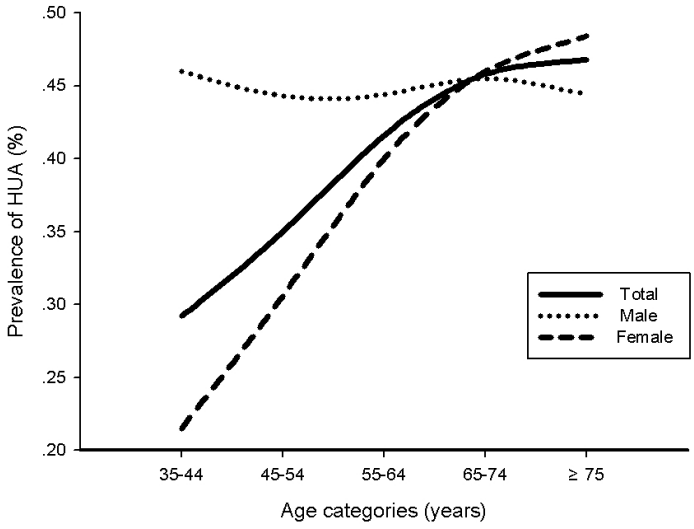
Figure legends

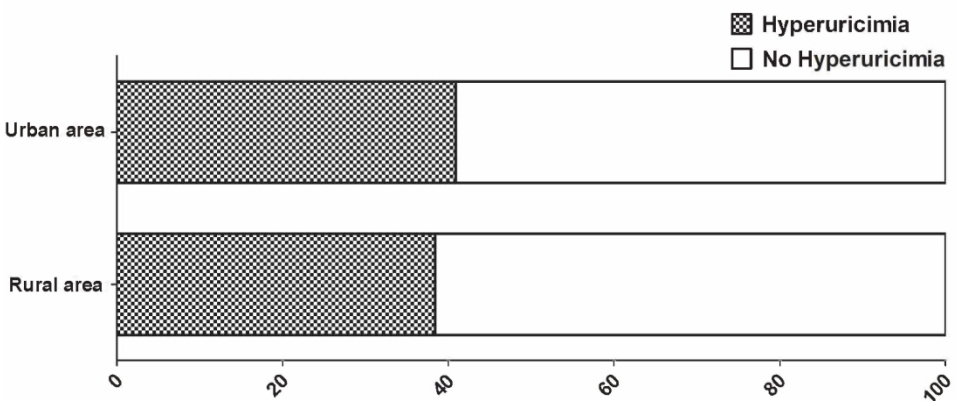
Figure 1. Differential prevalence of hyperuricemia (HUA) among men and women across 10-year age intervals starting at 35.

Figure 2. Prevalence of hyperuricemia in urban and rural areas.

Figure 3. Receiver operating characteristic (ROC) curves for determination of predictive value of hyperuricemia (HUA) or serum uric acid (SUA) for AF in men (A) and women (B). AUC (area under curve).



Different prevalence of HUA among male and female in stepwise age categories



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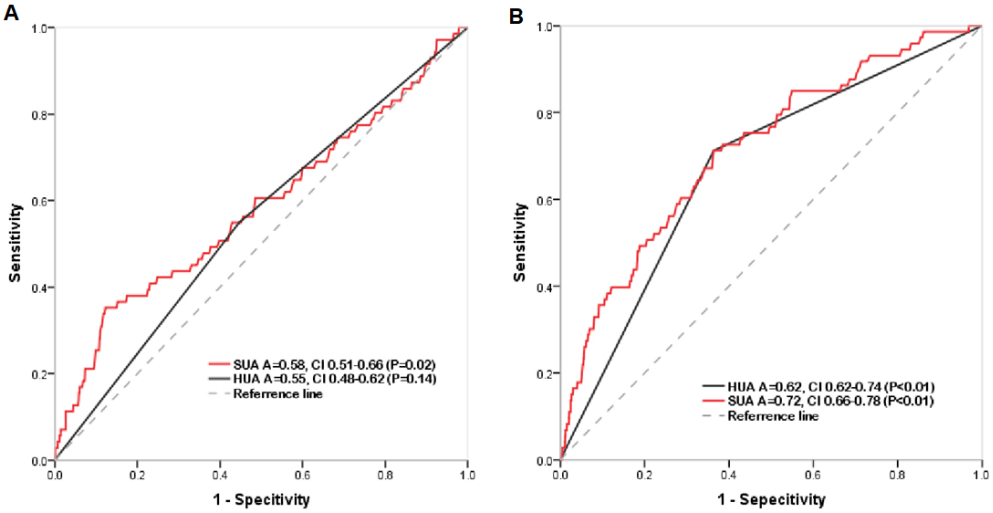

A, receiver operating characteristic (ROC) curve of HUA or SUA for AF in male; B, ROC curve of HUA or SUA for AF in female;

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract L48
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found L49-L63
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported L90-L100
Objectives	3	State specific objectives, including any prespecified hypotheses L101-L105
Methods		
Study design	4	Present key elements of study design early in the paper L109-L114
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection L115-137
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants L117-L123
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable L139-L155
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group L164-L173
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at L109-L114, L136-L137
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding L165-L166
		(*b*) Describe any methods used to examine subgroups and interactions L166-L171
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed L136-L137, L177-L179
		(b) Give reasons for non-participation at each stage L177-L179
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders L179-L191
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures L179-191
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included L206-L212, L228-L234
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives L242-L247
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias L312-L314
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence L249-L309
Generalisability	21	Discuss the generalisability (external validity) of the study results L317-L321
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based L336-L339

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou (China) Heart Study

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High prevalence of hyperuricemia and its impact on non-valvular atrial fibrillation: The cross-sectional Guangzhou (China) Heart Study

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ABSTRACT

Objectives: There are country and regional variations in the prevalence of hyperuricemia (HUA). The prevalence of HUA and non-valvular atrial fibrillation (NVAF) in southern China is unknown.

Design: A cross-sectional study.

Setting and participants: A total of 11,488 permanent residents aged 35 or older from urban and rural areas of Guangzhou, China were enrolled. A questionnaire was used to compile each participant's demographic information and relevant epidemiological factors for HUA and NVAF. All participants were assessed using a panel of blood tests and single-lead 24-hour electrocardiogram.

Main outcome measures: HUA was defined as serum uric acid level >420μmol/L in men and >360μmol/L in women. NVAF was diagnosed per guidelines.

Results： The prevalence of HUA was 39.6% (44.8% in men and 36.7% in women), and 144 residents (1.25%) had NVAF. Prevalence of HUA increased with age in women but remained stably high in men. After adjusting for potential confounders, age, living in urban areas, alcohol consumption, central obesity, elevated fasting plasma glucose level, elevated blood pressure, lower high-density lipoprotein cholesterol level and elevated triglycerides level were associated with increased risk of HUA. Residents with HUA were at higher risk for NVAF. Serum uric acid level had a modest predictive value for NVAF in women but not men.

Conclusions: HUA was highly prevalent among citizens of southern China and was a predictor of NVAF among women.

Strengths and limitations of this study:

- This cross-sectional population-based study investigated the prevalence of hyperuricemia and its impact on that of non-valvular atrial fibrillation.
- A large cohort from urban and rural areas of Guangzhou was studied.
- The surveyed areas were all randomized to increase reliability.
- Residents aged under 35 years were not included.
- The results of this cross-sectional study need to be validated in prospective studies.

INTRODUCTION

The prevalence of hyperuricemia (HUA) ranges from 13.3% to 21.6% and varies by sex and among countries or regions [1, 2]. Local differences are apparent within countries, likely influenced by environmental, climatic, economic status and especially dietary habits variations [3, 4]. Although several epidemiological studies reported an association between serum uric acid (SUA) level and cardiovascular conditions such as hypertension, coronary artery disease, vascular dementia, metabolic syndrome, cerebrovascular disease and kidney disease, it was not apparent in others such as the Framingham Heart Study [5].

Atrial fibrillation (AF), the most common clinical cardiac arrhythmia, contributes to increased morbidity and mortality especially in the setting of other cardiovascular risk factors [6]. AF disease burden is estimated to reach 9 million cases by 2050 in China [7], with the increasing prevalence of AF being a global health problem [8, 9]. HUA has been associated with AF [10-13]; however, prevalence of HUA and its potential association with that of non-valvular AF (NVAF) in the typical southern Chinese city of Guangzhou with its particular combination of dietary habits, economic status and climate remain undefined.

The present cross-sectional population-based study aimed to assess the prevalence of HUA and its association with NVAF among Guangzhou residents.

Materials and methods

Study population

We conducted a cardiovascular epidemiological survey (the Guangzhou Heart Study) from July 2015 to August 2017 in Guangzhou. Randomized multistage cluster sampling was used in this

study. We divide all the 11 districts in Guangzhou into 2 groups: urban group (Yuexiu, Haizhu, Liwan, Tianhe, and Huangpu District) and rurban group (Baiyun, Panyu, Nansha, Huadu, Conghua and Zengchen District). Sealed envelopes with the names of all the districts written on pieces of paper were prepared before the selection. Then, we randomly selected one envelope from each group. Yuexiu District was selected to represent the urban places while Panyu District was chosen for the rural regions. We selected Xinzao Town, Nancun Town and Xiaoguwei Street to conduct the survey in Panyu District using the same methods above while Dadong Street and Baiyun Street were chosen in Yuexiu District. Finally, in the same way, 7 residential committees in Dadong Street and Baiyun Street and 17 village committees in Xinzao Town, Nancun Town and Xiaoguwei Street based on population size. Every subject who was eligible to fit the inclusive criterions in Yuexiu and Panyu District was all included for the study.

The residents in the study sites were invited to participate in this study by 3-round mobilization via door-to-door visits or telephone appointments. For the first-round mobilization, we made appointments for the survey from door to door. Responsive information was collected to identify who were eligible to join the survey and within the eligible subjects who were willing, reluctant or indecisive to come. In the second-round mobilization, we promoted the residents who were not connected in the same way. At the same time, we continued to have telephone appointments for people who were willing or indecisive to join the survey but had not come yet and collected the responsive information. During the last round of the mobilization, we mainly made telephone appointments for the eligible rest of the list who still did not come and sum up the latest responsive information. Residents were enrolled if they met all of the following inclusion criteria: 1) registered in the Guangzhou Household Register; 2) aged 35 years or older; and 3) living in

the selected communities for at least 6 months by the day they participated in the survey. Residents were excluded if they had any of the following conditions: 1) mental or cognitive disorders including dementia, disturbance of understanding, and deaf-mutters; 2) mobility difficulties including paraplegia; 3) pregnant or lactating women; 4) malignant tumors under treatment; 5) temporary residents including renters; or 6) non-responders during the 3-round mobilization.

This study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association (No. GDREC2015306H) and was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All residents needed to sign an informed consent prior to the initiation of the study.

Data collection

A structured and interviewer-administered questionnaire was used to survey each participant's demographic information, medical history, social habits, family history and emotional status. Physical examination including measurement of waist circumference, height, weight, blood pressure, heart rate and body fat was performed using standard instruments and protocols. Blood samples were collected and tested following standardized procedures by an authorized medical laboratory. Electrocardiogram (ECG) and 24-hour single-lead ECG were recorded for each participant and reports were assessed by two independent cardiologists; methodological details were as reported by Deng et al. [14]. A total of 29,196 residents were eligible for inclusion, of whom 12,013 residents participated in the study; the response rate was therefore 41.16%.

Cohort definition

Subjects were diagnosed with NVAF if they met any of the following criteria: 1) AF pattern in ECG screening; 2) No AF in ECG screening but positive AF history; and 3) AF episodes in 24 hours single-lead ECG recording. All residents with atrial fibrillation underwent cardiac ultrasonography to assess for valvular AF. NVAF was diagnosed as per guidelines [6]. ECG and single-lead 24 hours ECG recordings were performed by well-trained physicians, and AF diagnosis was made by two specific electrophysiological experts. HUA was defined as serum uric acid (SUA) level >420μmol/L in men and >360μmol/L in women. The metabolic syndrome (MetS) was defined as having at least three out of the five following characteristic signs [7]: abdominal obesity (defined as waist circumference ≥90cm for men and ≥80cm for women); elevated triglycerides level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality; reduced high-density lipoprotein (HDL) cholesterol: < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality; elevated blood pressure (BP): systolic BP > 130 mmHg or diastolic BP > 85 mmHg, or treatment for previously diagnosed hypertension; and elevated fasting plasma glucose (FPG): FPG > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes mellitus.

Patient and Public Involvement

Residents were not involved in the development of the research question and outcome measures. All residents were informed of their right to enquire about their data and test results. If residents were diagnosed with cardiovascular disease, they were notified by phone to present themselves to Guangdong General Hospital for further treatment.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as number (percentage). Comparisons between groups were made using the Student *t* test or chi-square tests, as appropriate. Multivariable logistic regression models were developed to investigate the risk factors for HUA and the associations between the prevalence of NVAF and HUA. Odds ratio (OR) and corresponding 95% confidence interval (95% CI) were calculated to assess the associations. Receiver-operating characteristic (ROC) analyses were used to calculate the predictive value of SUA and HUA for NVAF. SAS software version 9.3 (SAS Institute Inc.; Cary, NC) was used for the statistical analyses. All statistical tests were 2-sided, and a $P<0.05$ was statistically significant.

RESULTS

Baseline characteristics

A total of 12,013 patients were enrolled in the study; 175 patients had atrial fibrillation, which was of valvular origin in 31. A total of 494 patients refused to have a blood test., and therefore 11,488 patients were included in the statistical analysis. The prevalence of HUA was 39.6% (44.8% in men and 36.7% in women, Table 1). Prevalence of HUA increased with age in women but maintained a steady high level in men [Figure 1]. The prevalence of HUA in urban areas was higher than in rural areas (40.9% vs 38.6%, respectively, P=0.003, Figure 2). Based on medical history, the proportion of men with HUA was significantly higher than that of women. Residents with HUA were significantly older. Regardless of gender, abdominal circumference and body

mass index were significantly greater in residents with HUA. A higher proportion of NVAF, HTN, DM, central obesity, and stroke/transient ischemic attack (TIA) were observed in residents with HUA. In laboratory testing, hemoglobin (HGB), platelet count (PLT), red blood cell count (RBC), and levels of low-density lipoprotein (LDL), cholesterol (CHOL), and fasting plasma glucose (FGP) were significantly higher while those of creatinine and high-density lipoprotein were significantly lower in residents with HUA. Significant larger proportion of reduced HDL cholesterol, elevated TG level and MetS were observed in residents with HUA.

Table1 Baseline characteristics of residents with or without Hyperuricemia

	Total (*n*=11488)	HUA (*n*=4547)	No HUA (*n*=6941)	*P*-value
Clinical characteristics				
Male (n, %)	4047(35.2)	1814(39.9)	2233(32.2)	<0.01
Age (yrs)	58.22±11.74	59.98±11.44	57.06±11.79	<0.01
Urban (n, %)	5403(46.9)	2210(48.6)	3193(46.0)	0.01
Systolic Bp (mmhg)	130.51±20.52	134.16±20.39	128.13±20.25	<0.01
Diastolic Bp (mmhg)	80.70±11.61	82.30±11.60	79.62±11.49	<0.01
Non-valvular AF (n, %)	144(1.3)	91(2.0)	53(0.8)	<0.01
Hypertension (n, %)	3377(29.4)	1744(38.4)	1633(23.5)	<0.01
Diabetes mellitus (n, %)	1050(9.1)	528(11.6)	522(7.5)	<0.01
Elevated BP (n, %) &	6698(58.3)	3092(68.0)	3606(52.0)	<0.01
BMI (kg/m^2)	24.01±3.55	25.08±3.55	23.32±3.37	<0.01
Abdominal circumference (cm)	84.41±10.10	87.69±9.61	82.26±9.83	<0.01
Male	84.41±10.11	87.71±9.63	82.26±9.83	<0.01
Female	82.76±9.98	86.36±9.64	80.66±9.56	<0.01
Central obesity (n, %) §	6183(53.8)	2984(65.6)	3199(46.1)	<0.01
Heart failure (n, %)	114(1.0)	50(1.1)	64(0.9)	0.39

Stroke/TIA (n, %)	274(2.4)	128(2.8)	146(2.1)	0.02
Alcohol consumption (n, %)	2467(21.5)	1060(23.3)	1391(20.0)	<0.01
Smoking (n, %)	2451(21.3)	1114(24.5)	1353(19.5)	<0.01
Laboratory examinations				
HGB (g/L)	138.74±14.07	140.14±14.11	137.83±13.97	<0.01
PLT (10^9/L)	243.78±60.67	245.42±61.76	242.71±59.93	0.019
RBC (10^{12}/L)	4.76±0.64	4.80±0.65	4.73±0.63	<0.01
HDL cholesterol(mmol/L)	1.49±0.55	1.36±0.51	1.58±0.56	<0.01
Reduced HDL cholesterol (n, %) □	2589(22.5)	1369(30.1)	1220(17.6)	<0.01
LDL (mmol/L)	3.64±1.03	3.72±1.04	3.58±1.01	<0.01
CHOL (mmol/L)	5.486±1.13	5.57±1.17	5.42±1.11	<0.01
TG (mmol/L)	1.696±1.43	1.47±1.06	2.05±1.18	<0.01
Raised TG level (n, %) £	3787(33.0)	2140(47.1)	1647(23.7)	<0.01
FPG (mmol/L)	5.586±1.57	5.69±1.52	5.51±1.60	<0.01
Elevated FPG (n, %) ¶	3375(29.4)	1653(36.4)	1722(24.8)	<0.01
Uric acid (umol/L)	367.20±98.39	460.60±72.77	306.01±55.62	<0.01
Male	367.00±98.30	460.60±72.70	306.01±55.63	<0.01
Female	340.76±89.40	434.37±64.43	286.30±46.52	<0.01
Creatinine(umol/L)	76.89±25.45	83.78±33.25	72.36±17.22	<0.01

BP: Blood pressure; TIA: Transient Ischemic Attack; BMI: Body Mass Index; HGB: Hemoglobin; PLT: Platelet; RBC: Red blood cell counts; FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL: Cholesterol; Mets: Metabolic syndrome

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.

Analysis of prevalence risk of hyperuricemia.

We performed logistic regression analyses to evaluate the risk factors for hyperuricemia (Table

2). After adjusting for possible confounders, age (per 10years, OR 1.10, 95% CI 1.06-1.14), living region (urban, OR 1.15, 95% CI 1.06-1.25), alcohol consumption (OR 1.12, 95% CI 1.01-1.24), central obesity (OR 1.82, 95% CI 1.67-1.99), elevated FPG (OR 1.18, 95% CI 1.08-1.29), elevated BP (OR 1.34, 95% CI 1.22-1.46), reduced HDL (OR 1.27, 95% CI 1.15-1.71), and elevated triglycerides level (OR 2.14, 95% CI 1.97-2.35) were strongly associated with risk for hyperuricemia.

Table2. Analysis of prevalence risk of hyperuricemia in multiple logistic regression model.

Model‡	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	1.10	1.06-1.14	<0.01
Living area(urban)	1.15	1.06-1.25	<0.01
Alcohol consumption	1.12	1.01-1.24	0.03
Central obesity §	1.82	1.67-1.99	<0.01
Elevated FPG ¶	1.18	1.08-1.29	<0.01
Elevated BP &	1.34	1.22-1.46	<0.01
Reduced HDL □	1.27	1.15-1.41	<0.01
Raised Triglycerides level £	2.14	1.96-2.35	<0.01

FPG: fasting plasma glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHOL: Cholesterol;

‡ Adjusted risk factors: age (per 10years), living region, education level, marriage status, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level

§: Central obesity was defined as waist circumference >85cm for men and >80cm for women

¶: Elevated FPG was defined as fasting plasma glucose > 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

&: Elevated BP was defined as systolic BP > 130 or diastolic BP > 85 mm Hg or history of hypertension

□: Reduced HDL was defined as HDL <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women or specific treatment for this lipid abnormality.

£: Raised Triglycerides level was defined as Triglycerides > 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid

abnormality.

Predictive value of hyperuricemia on non-valvular AF.

The adjusted multivariable logistic regression analysis showed that age (per 10 years) (OR 2.31, CI 1.93-2.78), female gender (OR 2.21, CI 1.45-3.36), central obesity (OR 1.93, CI 1.29-2.90,P<0.01), HUA (OR 2.19, 95% CI 1.53-3.12) and history of heart failure (OR 5.13, CI 2.52-10.43) were risk factors for AF prevalence (Table 3). ROC curves were generated for SUA by gender to determine its diagnostic capability for NVAF. The area under the ROC curve (AUC) for SUA was 0.72 (95% CI: 0.79–0.91) in women and 0.58 (95% CI: 0.51–0.62) in men [Figure 3].

Table3. Increasing odds ratio for non-valvular AF with hyperuricemia.

Variables[ω]	Odds ratio	95% confidence interval	*P*-value
Age (per 10years)	2.31	1.93-2.78	<0.01
Gender(female)	2.21	1.45-3.36	<0.01
Central obesity	1.93	1.29-2.87	<0.01
HUA	2.19	1.53-3.12	<0.01
Heart failure	5.13	2.53-10.43	<0.01

AF: atrial fibrillation; HUA: Hyperuricemia

ω Adjusted risk factors: age (per 10years), gender, heart failure, smoking status, alcohol consumption, central obesity, Elevated FPG, Elevated BP, Reduced HDL, Raised Triglycerides level and Hyperuricemia

DISCUSSION

The present study had three main findings. Firstly, the prevalence of HUA was 39.6% (44.8% in men and 36.7% in women) with sex related differences in residents with HUA. Secondly, the age,

living in urban, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL, and elevated triglycerides level were strongly associated with risk of HUA. Thirdly, residents with HUA had a markedly increased risk of NVAF, and SUA had moderate predictive value for NVAF only in women.

The prevalence of hyperuricemia

Regional differences in prevalence of HUA have been reported. According to Liu's review [15], the prevalence of HUA in mainland China from 2000-2014 was 13.3% (19.4% in men and 7.9% in women). In Chinese publications, prevalence of HUA in Guangdong province ranged from 15 to 20% [15]. The National Health and Nutrition Examination Survey (NHANES) in the United States documented a 21.2% HUA prevalence in men and 21.6% in women [2] which was similar to that in Japan and Taiwan [16, 17]. In this study, the prevalence of HUA in Guangzhou area was 39.6% (44.8% in men and 36.7% in women), which was considerably higher than that in previous reports. The traditional dietary habits of Guangzhou residents might be one of the important reasons. Sex related differences in HUA prevalence also were observed in our study. The prevalence of HUA increased with age in women while remaining at a steady high level in men regardless of age. A rapidly increasing prevalence of HUA in women older than 55 years old was observed; the prevalence was similar to or even higher than that of men after 65 years old. The latter finding might reflect greatly decreased estrogen level in postmenopausal women [18]. Estrogen might promote excretion of SUA via its effect on post-secretory tubular reabsorption of SUA, as confirmed by the effectiveness of hormone replacement therapy in reducing SUA [19, 20].

Risk factors of hyperuricemia

Due to the increasing prevalence of HUA, it is of great clinical significance to search for its risk factors. Risk factors for hyperuricemia might vary among ethnic groups. In this study, age, alcohol consumption, central obesity, elevated FPG, elevated BP, reduced HDL and elevated triglycerides level were strongly associated with the risk of HUA. Previous studies showed that hypertriglyceridemia was strongly associated with risk of HUA [21]. Consistent with our study, the Seychelles Heart Study II documented that high serum TG level was the strongest predictor of HUA [22]. The mechanism of hypertriglyceridemia leading to HUA might be related to lifestyle [22] or genetic factors [23]. Central obesity, elevated FPG, elevated BP, reduced HDL and elevated triglycerides level are all diagnostic components of MetS; therefore, hyperuricemia was closely related to MetS. Yuan's study showed that MetS was 10 times higher in individuals with SUA ≥10 mg/dL than in adults with SUA <6 mg/dL and normal body mass index [24]. A meta-analysis of more than fifty-four thousand participants showed that elevated SUA was associated with increased risk of MetS [25]. SUA and MetS often accompany each other and promote the occurrence of cardiovascular disease.

Hyperuricemia and non-valvular atrial fibrillation

HUA showed a strong relationship with AF in our study. As reported previously, HUA was associated with endothelial dysfunction, oxidative stress, abnormal high levels of inflammatory markers and insulin resistance [26-28]. In the Atherosclerosis Risk In Communities (ARIC) study [29], HUA was associated with a greater risk of new onset AF. In contrast to our study, the ARIC study enrolled patients aged 45 to 64 years. Another study from Taiwan [30] showed that SUA

significantly correlated with left atrial diameter and that HUA was a significant risk factor for new-onset AF in multivariable Cox regression analysis; however, HUA was diagnosed only when individuals suffered from a gout attack, while in the present study asymptomatic patients were not excluded and uric acid metabolism status of residents was assessed by measuring blood uric acid levels in the fasting state. A recent Chinese report also showed that HUA increased AF risk by 2-fold among elderly southwestern residents [31]. Only 7.6% AF residents in the latter study presented with HUA while 63.2% did not so in the present study cohort. Mechanisms underlying the association between uric acid level and AF remain unclear; however, elevated UA has been associated with vasoconstriction, vascular smooth muscle cell proliferation, endothelial dysfunction, oxidative stress, local inflammation and insulin resistance[32].

Differences in cardiovascular events rates by gender have been reported[33]. In the study by Suzuki and the Atherosclerosis Risk in Communities (ARIC) Study, elevated SUA was associated with a higher risk of AF particularly in women. Both SUA and HUA had moderate predictive value for AF in the present study. It is worth noting that SUA had higher AUC than HUA, which indicates a better predictive value for AF for continuous rather than a cutoff for uric acid (UA). As reported previously, the relationship between UA and cardiovascular disease is apparent with normal to high UA serum level (310-330umol/L) [34-36]; each 1mg/ml increase in UA level was associated with 12% to 20% increase in the risk for cardiovascular and all-cause mortality, respectively [37]. Therefore, UA level might be strongly associated with AF. The bases for sex related differences in HUA and AF remain unknow. HUA has been associated with endothelial dysfunction in post-menopausal women, suggesting that HUA could be an independent risk factor for cardiovascular disease including AF, particularly among

postmenopausal women [38].

Limitations

The present study is limited by its cross-sectional design, warranting prospective studies with appropriate follow-up to validate findings; and lack of inclusion of residents aged under 35 years whose HUA prevalence remains unknown.

CONCLUSIONS

This large-scale cross-sectional study demonstrated a high prevalence of HUA with sex related differences among Guangzhou residents. Increasing age, living in an urban setting, alcohol consumption and components of MetS increase the risk of HUA. Residents with HUA had a markedly increased risk for AF and the uric acid level had moderate predictive value for NVAF only in women.

Contributors

W.L., H.D., Y.X. and S.W. conceived the study, analyzed data, interpreted results and drafted the manuscript. P.G., R.C., F.L., X.F., X.Z., H.L., W.H., Y.L., F.W., M.Z., H.L, J.H., W.W. collected data and completed the survey.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship or publication of this article.

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DATA SHARING STATEMENT

The data are available from the corresponding author upon reasonable request.

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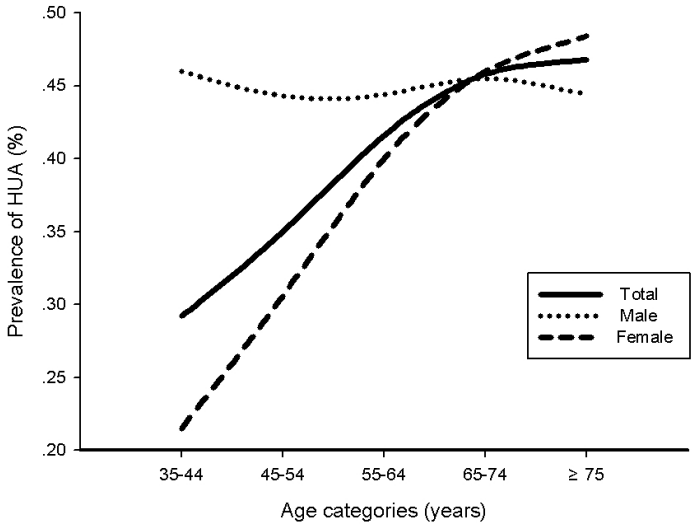
Figure legends

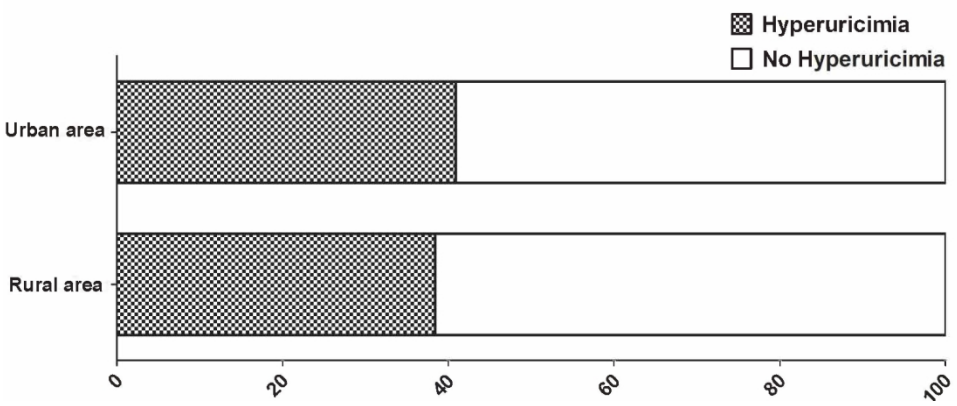
Figure 1. Differential prevalence of hyperuricemia (HUA) among men and women across 10-year age intervals starting at 35.

Figure 2. Prevalence of hyperuricemia in urban and rural areas.

Figure 3. Receiver operating characteristic (ROC) curves for determination of predictive value of hyperuricemia (HUA) or serum uric acid (SUA) for AF in men (A) and women (B). AUC (area under curve).



Different prevalence of HUA among male and female in stepwise age categories



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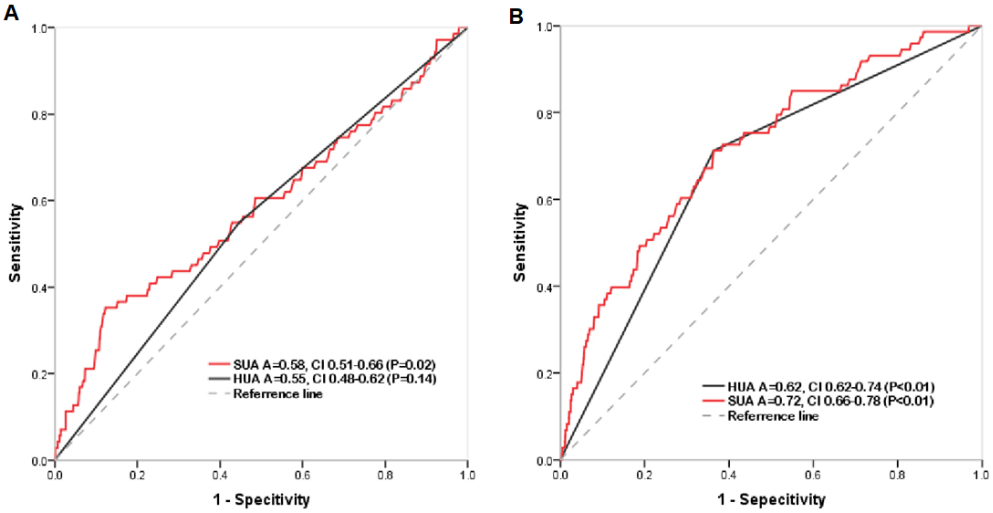

A, receiver operating characteristic (ROC) curve of HUA or SUA for AF in male; B, ROC curve of HUA or SUA for AF in female;

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract L48
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found L49-L63
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported L90-L100
Objectives	3	State specific objectives, including any prespecified hypotheses L101-L105
Methods		
Study design	4	Present key elements of study design early in the paper L109-L114
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection L115-137
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants L117-L123
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable L139-L155
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group L164-L173
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at L109-L114, L136-L137
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding L165-L166
		(*b*) Describe any methods used to examine subgroups and interactions L166-L171
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed L136-L137, L177-L179
		(b) Give reasons for non-participation at each stage L177-L179
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders L179-L191
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures L179-191
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included L206-L212, L228-L234
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives L242-L247
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias L312-L314
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence L249-L309
Generalisability	21	Discuss the generalisability (external validity) of the study results L317-L321
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based L336-L339

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.