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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Abstract

Objectives: Hyperuricemia has been reported to be significantly associated with risk of obesity. However, previous studies on the association between serum uric acid (SUA) and body mass index (BMI) yielded conflicting results. The present study examined the relationship between SUA and obesity among Chinese adults.

Methods: Data were collected at Guangdong Second Provincial General Hospital in Guangzhou City, China between January 2010 and December 2018. Participants with medical checkup ≥2 times were included in our analyses. Physical examinations and laboratory measurement variables were obtained from the medical checkup system. The high SUA level group was classified as participants with hyperuricemia, and obesity was defined as BMI≥28kg/m^2. Logistic regression model (LRM) was performed for data at baseline. For all participants, generalized estimation equation (GEE) model was used to assess the association between SUA and obesity, where the data were repeatedly measured over the nine-year study period. Subgroup analysis was performed by gender and age group. We calculated the cut-off values for SUA of obesity using the receiver operating characteristic curves (ROC) technique.

Results: A total of 15,959 participants (10,023 males and 5,936 females) were included in this study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic regression analysis at baseline, we observed a positive association between SUA and risk of obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeatedly measured over 9-year for all participants in GEE model, the per-SD OR was 1.85 (95% CI:1.77,1.91) for SUA and the increased risk of obesity was greater for male (OR=1.45) and elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant associations between SUA and obesity with higher risk in female (OR=2.35) and young participants (OR=1.87) when compared to male (OR=1.70) and the elderly participants

(OR=1.48). The SUA cut off points for risk of obesity using ROC curves were approximately consistent with the international standard.

Conclusions: Our study found higher SUA level was associated with increased risk of obesity. More high-quality research is needed to further support this finding.

Keywords: serum uric acid, obesity, generalized estimation equation model, risk factors, China

Strengths and limitations of this study

- This is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China.
- The study analysis was based on the GEE model which can increase the accuracy of the prediction.
- The results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.
- The younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

Introduction

An individual's health behavior can influence both physical health and ability to recover from an illness. Annual medical checkup is an example of a positive health behavior, as this preventative measure is associated with earlier disease detection, greater treatment success, and faster recovery from a disease [1]. For this reason, medical data obtained from primary care is a useful source as it includes information on symptoms and healthcare utilization, all beneficial for use in prediction analysis. Medical checkup data often includes a variety of diagnostic tests to assess health status for early detection and disease prevention. Additionally, medical checkup data provides valuable information on present and past health conditions that are generally difficult to obtain in most population-based data [2]. More specifically, medical checkup data is a reliable and objective measure for identifying chronic diseases such as hyperuricemia and obesity.

Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting in hyperuricemia [3, 4]. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and 7.9% for women [5]. Additionally, in 2019 the obesity prevalence was nearing 12% in China. Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was reported to be independently correlated with changes in uric acid concentration, there might be an interaction between them as suggested in prior pathophysiological and metabolic studies [6]. Epidemiological and clinical evidence supports a strong significant positive association between SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq [7]. A cross-sectional study showed that body mass index (BMI) significantly increases with elevated SUA among 27,009 middle-aged and elderly Chinese adults [8]. Previous research showed that hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis [9]. With the increasing prevalence of obesity among adults with hyperuricemia, it is of public health importance to evaluate the long-term epidemiological transitions to develop policies centered on intervention.

Numerous trend analyses have reported the association between SUA and BMI based on short-term survey data in China [10, 11]. However, there remains a gap in evidence regarding the long-term trend for providing estimates on the risks of obesity among Chinese adults during the last two decades. Therefore, the present study aimed to examine the relationship between SUA and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

Methods

Study design and subjects

We conducted a large retrospective study in China. Medical examinations were performed in 2010 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical checkup; (2) absence of blood biochemical examination; and (3) no documented information on BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

Measurements

All participants were invited to participate in an in-person evaluation which included physical examination and laboratory testing. Physical examinations were conducted following a standardized protocol, including weight, height, waist circumference, hip circumference, and blood pressure. Waist circumference was measured around the midway between the lowest border of the ribs and iliac crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated measurements in the presence of researchers. Laboratory measurements were obtained to measure SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).

Outcomes and definitions

Hyperuricemia was defined as having SUA concentrations>7.0 mg/dL (416.4μmol/L) in men or>6.0 mg/dL (356.9μmol/L) in women [12, 13]. SUA levels were categorized into two groups (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The high SUA level group was classified as participants with hyperuricemia. BMI was defined as weight divided by height^2 (kg/m^2). Meanwhile, it was categorized into two groups (non-obese [< 28 kg/m^2] and obese [≥28kg/m^2]) based on the Asia-Pacific criteria set by the World Health Organization [14, 15]. We excluded patients taken drugs that might affect uric acid metabolism, such as losartan, furosemide, and allopurinol. This study was approved by the Guangdong Second Provincial General Hospital.

Statistical analysis

We conducted descriptive analysis examining baselines participants. Continuous variables were reported as mean±standard derivation and categorical variables as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese and non-obese) were performed using Student t-tests for continuous variables and Chi-square analyses for categorical data. Logistic regression model (LRM) was used to evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also utilized generalized estimating equations (GEE) models with unstructured correlation structures to quantify their association between SUA and risk of obesity [16], given the data on SUA and obesity were repeatedly measured over the 9-year study period. All the models were adjusted for age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 μmol/L or per-SD increase in SUA.

We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age group (young <65 years vs. elderly ≥65 years). Additionally, we calculated the cut-off values of SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on the

criteria including that (1) the point on the curve with minimum distance from the left-upper corner of the unit square; and (2) the point where the Youden's index is maximum [17]. A two-sided p-value less than 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

There was no patient and/or public involvement in the design of the study.

Results

There were 15,959 participants (10,023 males) included in this study. The average number of health checkup for each participant was 2.62. The participants had a mean age of 37.38 (SD: 13.27) and a mean SUA of 367.05 (SD: 97.97) at baseline, respectively. There were 1,227 (7.6%) participants that were obese at baseline. Significant differences between the obese and non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR (p-value < 0.001) **(Table 1)**. In total, the prevalence of obesity was approximately 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males when compared to females. However, the prevalence had no obvious trend for different age groups (**Table 2**). The prevalence of obesity significantly increased with the number of medical checkup years in the group with high SUA and normal SUA level (p<0.001 for trend) (**Figure 1**).

As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for SUA [per-1 OR=1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.84 (95% CI: 1.77,1.90)], age [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic regression analysis (Model 1). When converted to categorical analysis, the OR value for SUA was greater for high level SUA compared to normal SUA. Additionally, the OR value was higher for

elderly than young participants. Likewise, in the multivariable GEE model (Model 2) based on all medical checkup participants, consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1 OR= 1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.85 (95% CI: 1.77,1.91)] for SUA, OR =1.45 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by categorical variables, we observed similar results with higher risk in male and elderly participants.

As shown in **Table 4**, similar results for GEE model analyses were observed in subgroup analyses. Significant associations between SUA and obesity were observed, where female [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an elevated risk. To calculate the discrimination ability of SUA among obese participants at different times of medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the overall cut-off values of SUA in males were 429.5μmol/L (range: 411.5-488.5 μmol/L) and in females were 326.9μmol/L (range: 298.5-426.5 μmol/L) when stratified by different times of medical checkups. Similarly, we calculated the overall cut-off values for SUA , which was 429.5 μmol/L (range: 366.7-431.5 μmol/L) in males and was 326.9 μmol/L (range: 301.5-362.1 μmol/L) in females when stratified by different years of medical checkups.

Discussion

To the best of our knowledge, this is the first longitudinal study that estimated the relationship between SUA and obesity over a long time period in China. The prevalence of obesity was approximately 14.2% for high SUA level. Previous studies found the prevalence of hyperuricemia ranges from 2.5 to 25 % depending on the study population country [18]. For instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand [19, 20]. Overall, we found high SUA level was associated with increased risk of obesity, within OR value of 1.85

(1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies [21, 22]. Currently, obesity and hyperuricemia, as well as their associated health complications (e.g. metabolic syndrome) have emerged as a major public health concern as a result of the growing prevalence, and the estimated economic burden [7].

Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity, suggesting the influence of overproduction and poor renal excretion [23]. Prior studies reported that increase SUA level is closely related to excessive production of UA and the reduction of urinary uric acid excretion and clearance [24]. Ultimately leading to increased risk of patients with visceral fatty obesity [23]. Visceral fat accumulation (VFA) results in a large influx of plasma free fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and subsequently produced large amounts of UA through the activated UA synthesis pathway [25, 26]. Additionally, many researchers have reported a significant correlation between VFA and BMI [27, 28]. Therefore, because of the close biological relationship between UA and BMI, it is of great importance for preventive medicine to pay attention to the interaction between UA and BMI.

Conflicting results regarding gender and age differences for the association between SUA and obesity have been reported [10, 29]. Our study found significant differences in obesity participants with elevated OR value among high SUA level, male, and elderly for all medical checkup participants. A similar study reported a positive relationship between BMI and SUA levels among healthy individuals in China [30]. Nevertheless, in this study the subgroup analyses showed that significant associated risk between SUA and obesity were observed higher in female and young participants. This is consistent with a Thailand study that reported high SUA concentrations were associated with greater risk of obesity in females [31]. However, a Bangladeshi study and a Japanese study reported that elevated SUA predicted obesity higher in males and the elderly[8, 29, 31]. Perhaps the associations of SUA with obesity varies based on population. Moreover, in a 10-year follow-up study, BMI was observed to significantly increase with higher SUA levels regardless of race

and gender [32]. Therefore, greater attention should be provided to these vulnerable populations in clinical guidelines.

An important observation was that the association between SUA and risk of obesity in the LRM [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in GEE model [OR= (1.85 (1.77,1.91)] for 9-year all participants. The risk of obesity within hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can be reflected the development of chronic diseases [33]. Regarding the assessment of cut-off values from receiver operating curves (ROC) of SUA in obesity participants, the cut-off values of SUA in males was 429.5μmol/L and in females was 326.9μmol/L in stratified analysis by times or years of medical checkup. The cut-off value was approximately consistent with the international standard for males [34]. However, it was underestimated for women in the group of obese participants. Perhaps the proportion of females were fewer in this study. The cut-off values of SUA in the study may be useful for on distinguishing tests among obesity and non-obesity participants, which were significant for certain risk value prediction and guidance[35].

We must note several limitations in the present study. First, the underlying mechanism by which SUA is increased in obese individuals remains not well understood. Second, this study did not collect information on whether participants were prescribed medication to treat hyperuricemia. Third, there are numerous confounding factors that have not been considered, which can be studied together with questionnaires in the future. Moreover, the younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

The present study has several strengths that must be noted. First, to our knowledge this is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China. Second, the study analysis was based on the GEE model with high quality data by controlling for confounding factors, which can increase the accuracy of the prediction. Third,

participants were representative of the general population with regard to clinical checkup and obesity status, enhancing the generalizability of our findings. Moreover, results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.

The present study filled current gaps in literature by analyzing the relationship between SUA and obesity using medical checkup data. We observed that medical checkup data can be used to improve risk of obesity prediction accuracy. The medical checkup data used in this study can help provide information that will facilitate intervention development and adoption at the individual level [36]. We believe that the utility of medical checkup data will reach beyond predictive power alone in the near future.

Conclusions

In conclusion, our study observed significant associations between SUA and obesity in this 9-year follow-up data. We mainly found higher SUA level was associated with increased risk of obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the number of medical checkup years in the groupof high SUA. Additionally, the increased risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses revealed significant associations between SUA and obesity with higher risk in female and young participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent with the international standard. More evidence from well-designed studies are needed to confirm our findings.

Author Contributions:

Guowei Li, Jie Zeng, Cheng Li: conceived and designed the study.

Guowei Li, Jie Zeng, Wayne R. Lawrence, Jun Yang: acquired data, performed statistical analyses and interpretation, and drafted the manuscript.

Junzhang Tian, Guanming Li, Wanmin Lian, Jingjun He, Hongying Qu, Xiaojie Wang: provided professional and statistical support, and made several critical revisions to the manuscript.

All authors read and approved the final manuscript.

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None declared.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

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Tables and Figure legends:

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Table 3. Relationship between risk factors and risk of obesity in the models.

Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Figure 1. Location of Guangdong Second Provincial General Hospital (Guangzhou, Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.

Figure 2. Flow diagram showing selection process of participants in our study.

Supplemental data:

Supplementary Figure 1. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different times of medical checkups.

Supplementary Figure 2. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different years of medical checkups (from 2010 to 2018).

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Characteristics	All patients	Obesity[a]	Non-obesity	*p*-value[b]
	n=15959	n=1227	n=14732	
SUA (μmol/L) [SD]	367.05 (97.97)	434.95 (97.65)	361.32 (95.82)	<0.001
Age (years) [SD]	37.38 (13.27)	40.40 (13.40)	37.13 (13.23)	<0.001
Male [n, (%)]	10023 (62.8)	1012 (82.5)	9011 (61.2)	<0.001
SBP (mmHg) [SD]	121.09 (15.85)	131.78 (16.47)	120.19 (15.47)	<0.001
DBP (mmHg) [SD]	73.84 (10.31)	81.16 (11.41)	73.23 (9.97)	<0.001
TC (mmol/L) [SD]	4.88 (0.93)	5.19 (0.95)	4.86 (0.93)	<0.001
TG (mmol/L) [SD]	1.46 (1.10)	2.18 (1.49)	1.40 (1.04)	<0.001
HDL-c (mmol/L) [SD]	1.26 (0.25)	1.15 (0.22)	1.27 (0.25)	<0.001
LDL-c (mmol/L) [SD]	2.92 (0.78)	3.20 (0.80)	2.90 (0.77)	<0.001
FPG (mmol/L) [SD]	5.06 (1.04)	5.51 (1.61)	5.03 (0.97)	<0.001
BUN (mmol/L) [SD]	4.78 (1.25)	5.07 (1.30)	4.75 (1.24)	<0.001
CR (mmol/L) [SD]	94.57 (17.12)	100.05 (16.17)	94.11 (17.12)	<0.001

Note: Continuous variables are presented as the means (standard derivation); SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr, creatinine.

[a] Obesity was defined as body mass index (BMI) ≥28.0 kg/m^2.

[b] *p* value for the difference of variables between the two datasets based on independent sample t-test or chi-square test.

*The average number of health checkup for each participant is 2.62.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Variable	Obesity prevalence, n (%) [a]		
	Normal SUA	High SUA	P-value
Gender			
Male	357/5280 (6.8)	570/3768 (15.1)	<0.001
Female	104/4431 (2.3)	97/937 (10.3)	<0.001
Age group			
<30	88/3509 (2.5)	168/1643 (10.2)	<0.001
30-44	182/3736 (4.9)	309/1692 (18.3)	<0.001
45-59	121/1727 (7.0)	125/865 (14.5)	<0.001
60-74	54/606 (8.9)	53/378 (14.0)	<0.001
≥75	11/134 (8.2)	12/127 (9.4)	<0.001
Overall	456/9711 (4.6)	669/4705 (14.2)	<0.001

Note: High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

[a]Obesity prevalence = (n of obesity) / (total participants).

Table 3. Relationship between risk factors and risk of obesity in the models.

Variable	Model 1[c]		Model 2[d]	
	OR[a] (95%CI[b])	*p*-value	*OR[a] (95%CI[b])*	*p*-value
Continuous analysis				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.84 (1.77,1.90)	<0.001	1.85 (1.77,1.91)	<0.001
Gender [n, (%)]				
Female	Reference		Reference	
Male	1.27 (1.16,1.39)	<0.001	1.45 (1.32,1.60)	<0.001
Age (years)	1.02 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001
Categorical analysis				
SUA[e]				
Normal SUA	Reference		Reference	
High SUA	2.02 (1.84, 2.23)	<0.001	2.57 (2.31, 2.87)	<0.001
Gender				
Female	Reference		Reference	
Male	1.25 (1.09, 1.43)	0.002	1.69 (1.59, 1.79)	<0.001
Age group				
<30	Reference		Reference	
30-44	1.38 (1.14, 1.66)	0.001	1.73 (1.54, 1.91)	<0.001
45-59	1.07 (0.89, 1.30)	0.475	1.94 (1.72, 2.18)	<0.001
60-74	1.12 (0.90, 1.38)	0.314	1.99 (1.72, 2.32)	<0.001
≥75	0.95 (0.71, 1.27)	0.718	1.86(1.50, 2.31)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model 1 was adjusted for the variables of SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on the first time of medical checkup participants by using multivariate logistic regression model (LRM).

[d]Model 2 was adjusted for the variables of repeated times or years of medical checkup, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

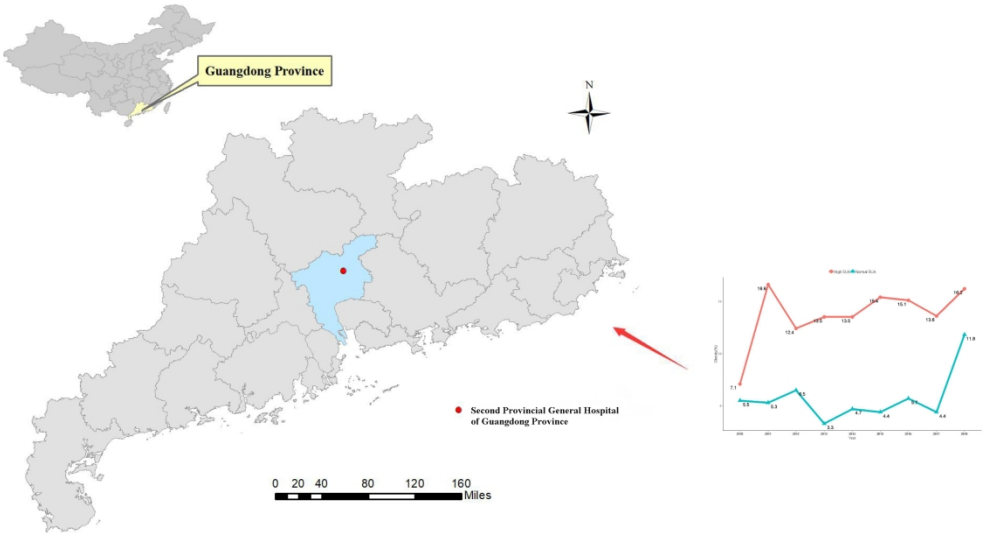
Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Variable	Generalized estimation equation model (GEE)[c]			
Gender	**Male**		**Female**	
	OR[a] (95%CI[b])	***p*-value**	***OR[a] (95%CI[b])***	***p*-value**
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.40 (2.23,2.59)	<0.001	3.79 (3.23,4.45)	<0.001
Age group	**Young (<65 year)**		**Elderly (≥65 year)**	
	OR[a] (95%CI[b])	***p-value***	***OR[a] (95%CI[b])***	***p-value***
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.00 (1.00,1.01)	<0.001
Per-SD	1.87 (1.80,1.94)	<0.001	1.48 (1.34,1.62)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.78 (2.58,2.99)	<0.001	1.99 (1.63,2.43)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.



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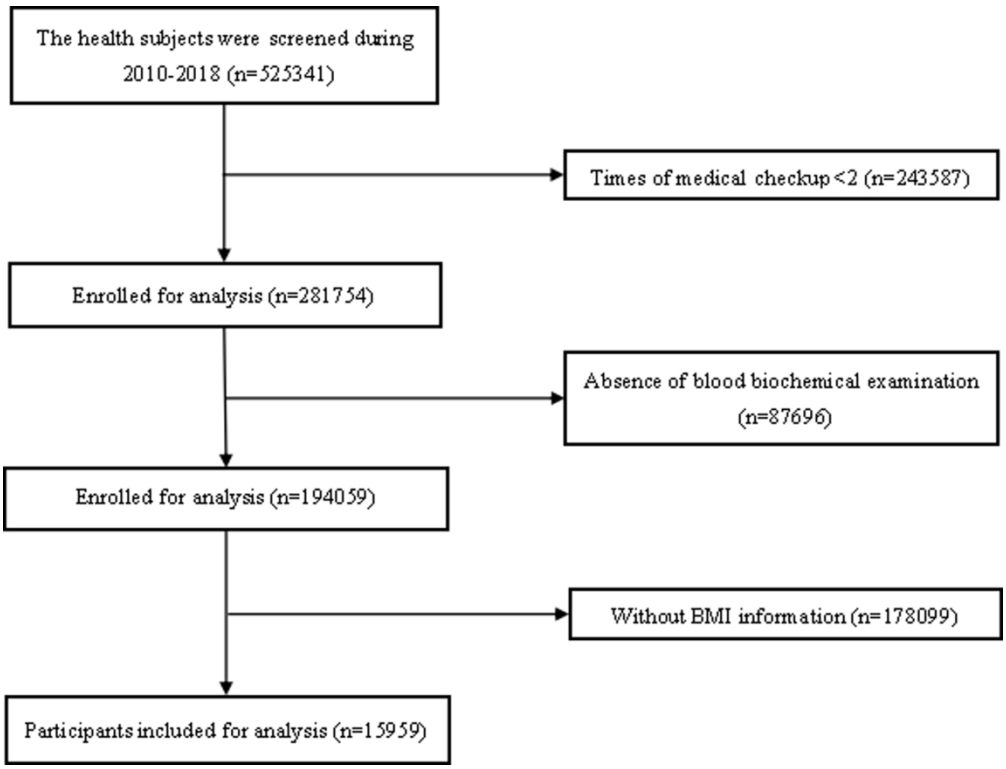

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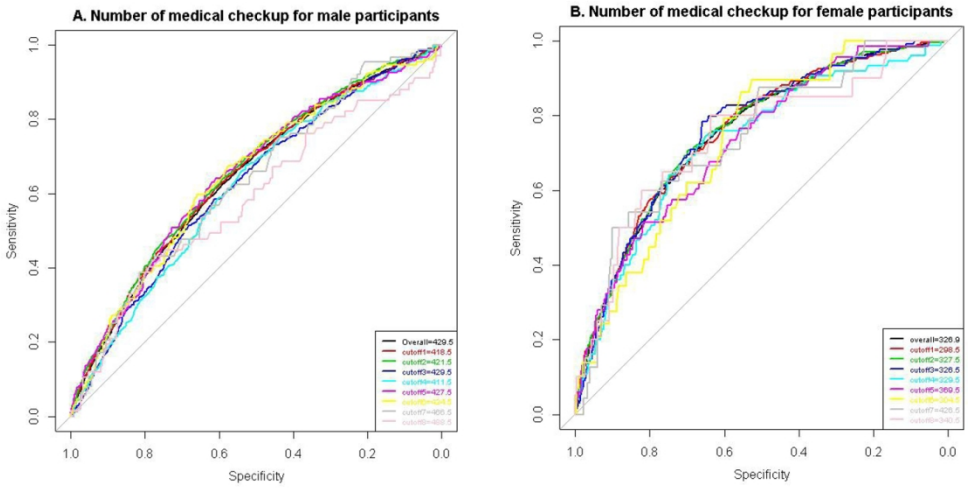

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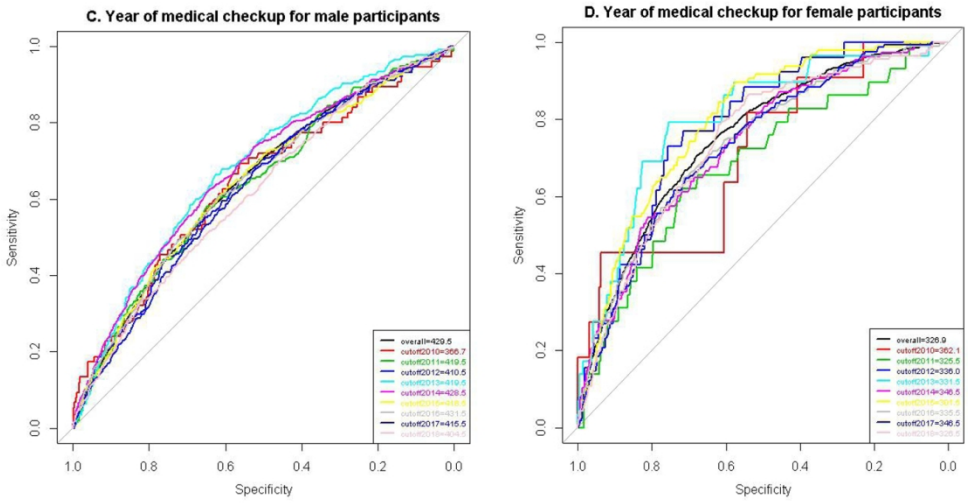

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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Abstract

Objectives: Hyperuricemia has been reported to be significantly associated with risk of obesity. However, previous studies on the association between serum uric acid (SUA) and body mass index (BMI) yielded conflicting results. The present study examined the relationship between SUA and obesity among Chinese adults.

Methods: Data were collected at Guangdong Second Provincial General Hospital in Guangzhou City, China between January 2010 and December 2018. Participants with ≥2 medical checkup times were included in our analyses. Physical examinations and laboratory measurement variables were obtained from the medical checkup system. The high SUA level group was classified as participants with hyperuricemia, and obesity was defined as BMI≥28kg/m^2. Logistic regression model (LRM) was performed for data at baseline. For all participants, generalized estimation equation (GEE) model was used to assess the association between SUA and obesity, where the data were repeatedly measured over the nine-year study period. Subgroup analyses were performed by gender and age group. We calculated the cut-off values for SUA of obesity using the receiver operating characteristic curves (ROC) technique.

Results: A total of 15,959 participants (10,023 males and 5,936 females) were included in this study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic regression analysis at baseline, we observed a positive association between SUA and risk of obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95% CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male (OR=1.45) and elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant associations between SUA and obesity with higher risk in female (OR=2.35) and young

participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48). The SUA cut off points for risk of obesity using ROC curves were approximately consistent with the international standard.

Conclusions: Our study observed higher SUA level was associated with increased risk of obesity. More high-quality research is needed to further support these findings.

Keywords: serum uric acid, obesity, generalized estimation equation model, risk factors, China

Strengths and limitations of this study

- This is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China.
- The study analysis was based on the GEE model which can increase the accuracy of the prediction.
- The results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.
- The younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

Introduction

An individual's health behavior can influence both physical health and ability to recover from an illness. Annual medical checkup is an example of a positive health behavior, as this preventative measure is associated with earlier disease detection, greater treatment success, and faster recovery from a disease [1]. For this reason, medical data obtained from primary care is a useful source as it includes information on symptoms and healthcare utilization, all beneficial for use in prediction analysis. Medical checkup data often includes a variety of diagnostic tests to assess health status for early detection and disease prevention. Additionally, medical checkup data provides valuable information on present and past health conditions that are generally difficult to obtain in most population-based data [2]. More specifically, medical checkup data is a reliable and objective measure for identifying chronic diseases such as hyperuricemia and obesity.

Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting in hyperuricemia [3, 4]. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and 7.9% for women [5]. Additionally, in 2019 the obesity prevalence was nearing 12% in China. Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was reported to be independently correlated with changes in uric acid concentration, there might be an interaction between them as suggested in prior pathophysiological and metabolic studies [6]. Epidemiological and clinical evidence supports a strong significant positive association between SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq [7]. A cross-sectional study showed that body mass index (BMI) significantly increases with elevated SUA among 27,009 middle-aged and elderly Chinese adults [8]. Previous research showed that hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis [9]. With the increasing prevalence of obesity among adults with hyperuricemia, it is of public health importance to evaluate the long-term epidemiological transitions to develop policies centered on intervention.

Numerous trend analyses have reported the association between SUA and BMI based on short-term survey data in China [10, 11]. However, there remains a gap in evidence regarding the long-term trend for providing estimates on the risks of obesity among Chinese adults during the last two decades. Therefore, the present study aimed to examine the relationship between SUA and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

Methods

Study design and subjects

We conducted a large retrospective study in China. Medical examinations were performed in 2010 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical checkups; (2) absence of blood biochemical examination; and (3) no documented information on BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

Measurements

All participants were invited to join an in-person evaluation that included physical examination and laboratory testing. Physical examinations were conducted following a standardized protocol, including weight, height, waist circumference, hip circumference, and blood pressure. Waist circumference was measured around the midway between the lowest border of the ribs and iliac crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated measurements in the presence of researchers. Laboratory measurements were obtained to measure SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).

Outcomes and definitions

Hyperuricemia was defined as having SUA concentrations>7.0 mg/dL (416.4μmol/L) in men or>6.0 mg/dL (356.9μmol/L) in women [12, 13]. SUA levels were categorized into two groups (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The high SUA level group was classified as participants with hyperuricemia. BMI was defined as weight divided by height^2 (kg/m^2) and categorized into two groups (non-obese [< 28 kg/m^2] and obese [≥28kg/m^2]) based on the Asia-Pacific criteria set by the World Health Organization [14, 15]. We excluded patients taken drugs that might affect uric acid metabolism, such as losartan, furosemide, and allopurinol.

Statistical analysis

We conducted descriptive analysis to present the characteristics of baselines participants. Continuous variables were reported as mean ± standard derivation (SD) and categorical variables as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese and non-obese) were performed using Student' t-tests for continuous variables and Chi-square analyses for categorical variables. Logistic regression model (LRM) was used to evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also utilized generalized estimating equations (GEE) models with unstructured correlation structures to quantify their longitudinal association between SUA and risk of obesity [16], given the data on SUA and obesity were repeatedly measured over the 9-year study period. All models were adjusted for age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 μmol/L or per-SD increase in SUA.

We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age group (youth <65 years vs. elderly ≥65 years). Additionally, we calculated the cut-off values of SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria including (1) the point on the curve with minimum distance from the left-upper corner of the unit

square; and (2) the point where the Youden's index is maximum [17]. A two-sided p-value less than 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

There were no patient and/or public involvement in the design of this study. The IRB approved the ethical waiver of informed consent for this study.

Results

There were 15,959 participants (10,023 males) included in this study. The average number of health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD: 13.27) and a mean SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. There were 1,227 (7.6%) participants that were obese at baseline. Significant differences between the obese and non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR (p-value < 0.001) **(Table 1)**. In total, the prevalence of obesity was approximately 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The prevalence of obesity significantly increased with the number of medical checkup years in the group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078 participants developed obesity over the 9-year period.

As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for SUA [per-1 OR=1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.84 (95% CI: 1.77,1.90)], age [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic regression analysis (Model 1). When converted to categorical analysis, the risks of obesity were

greater among those with high level of SUA, males and younger participants. Likewise, with longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2), consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1 OR= 1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.85 (95% CI: 1.77,1.91)] for SUA, OR=1.45 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by categorical variables, we observed similar results with higher risk in male and elderly participants.

As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup analyses. Significant associations between SUA and risk of obesity were observed, where female [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an elevated risk. To calculate the discrimination ability of SUA among obese participants at different times of medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the overall cut-off values of SUA were 429.5μmol/L (range: 411.5-488.5 μmol/L) in males and 326.9μmol/L (range: 298.5-426.5 μmol/L) in females when stratified by different times of medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5 μmol/L (range: 366.7-431.5 μmol/L) in males and 326.9 μmol/L (range: 301.5-362.1 μmol/L) in females when stratified by different years of medical checkups.

Discussion

To the best of our knowledge, this is the first longitudinal study that estimated the relationship between SUA and obesity over a long time period in China. The prevalence of obesity was approximately 14.2% for high SUA level. Previous studies found that the prevalence of hyperuricemia ranged from 2.5 to 25 % depending on the study population country [18]. For instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand [19, 20]. Overall, we found high SUA level was associated with increased risk of obesity, within OR

value of 1.85 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies [21, 22]. Currently, obesity and hyperuricemia, as well as their associated health complications (e.g. metabolic syndrome) have emerged as a major public health concern as a result of the growing prevalence, and the estimated economic burden [7].

Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity, suggesting the influence of overproduction and poor renal excretion [23]. Prior studies reported that increased SUA level is closely related to excessive production of UA and the reduction of urinary uric acid excretion and clearance [24]. This ultimately leads to increased risk of patients with visceral fatty obesity [23]. Visceral fat accumulation (VFA) results in a large influx of plasma free fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and subsequently produced large amounts of UA through the activated UA synthesis pathway [25, 26]. Additionally, many researchers have reported a significant correlation between VFA and BMI [27, 28]. Therefore, because of the close biological relationship between UA and BMI, it is of great importance for preventive medicine to pay attention to the interaction between UA and BMI.

Conflicting results regarding gender and age differences for the association between SUA and obesity have been reported [10, 29]. Our study found significant differences in obesity participants with elevated OR value among high SUA level, male, and elderly for all medical checkup participants. A similar study reported a positive relationship between BMI and SUA levels among healthy individuals in China [30]. Nevertheless, in this study the subgroup analyses showed that significant associated risk between SUA and obesity were observed higher in female and young participants. This is consistent with a Thailand study that reported high SUA concentrations were associated with greater risk of obesity in females [31]. However, study in Bangladesh and Japan reported that elevated SUA predicted obesity higher in males and the elderly[8, 29, 31]. Perhaps the associations of SUA with obesity varies by populations. Moreover, in a 10-year follow-up study, BMI was observed to significantly increase with higher SUA levels regardless of race and gender

[32]. Therefore, greater attention should be provided to those vulnerable populations in clinical guidelines.

An important observation was that association between SUA and risk of obesity in the LRM [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE model [OR= (1.85 (1.77,1.91)] for 9-year all participants. The risk of obesity within hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can reflect the development of chronic diseases [33]. Regarding the assessment of cut-off values from ROC of SUA in obesity participants, the cut-off values of SUA were 429.5μmol/L in males and 326.9μmol/L in females in stratified analysis by times or years of medical checkup. The cut-off value was approximately consistent with the international standard for males [34]. However, it was underestimated for women in the group of obese participants. Perhaps the proportion of females were fewer in this study. The cut-off values for SUA in the study may be useful for distinguishing tests among obesity and non-obesity participants, which were significant for certain risk value prediction and guidance[35].

We must note several limitations in the present study. First, the underlying mechanism by which SUA is increased in obese individuals remains not well understood. Second, this study did not collect information on whether participants were prescribed medication to treat hyperuricemia. Additionally, some medications used to treat hypertension may increase uric acid levels. Third, there are numerous confounding factors that have not been considered, which can be studied together with questionnaires in the future. Moreover, the younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

The present study has several strengths that must be noted. First, to our knowledge this is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China. Second, the study analysis was based on the GEE model with high quality data by

controlling for confounding factors, which can increase the accuracy of the prediction. Third, participants were representative of the general population with regard to clinical checkup and obesity status, enhancing the generalizability of our findings. Moreover, results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.

This study filled current gaps in literature by analyzing the relationship between SUA and obesity using medical checkup data. We observed that medical checkup data can be used to improve the risk of obesity prediction accuracy. The medical checkup data used in this study can help provide information that will facilitate intervention development and adoption at the individual level [36]. The utility of medical checkup data can potentially reach beyond predictive power alone in the near future.

Conclusions

In conclusion, our study observed significant associations between SUA and obesity in this 9-year longitudinal study. We mainly found higher SUA level was associated with increased risk of obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the number of medical checkup years in the group with high level of SUA. Additionally, the increased risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses revealed significant associations between SUA and obesity with higher risk for females and young participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent with the international standard. More evidence from well-designed studies are needed to confirm our findings.

Author Contributions:

Guowei Li, Jie Zeng, Guanming Li: conceived and designed the study.

Guowei Li, Jie Zeng, Wayne R. Lawrence, Jun Yang: acquired data, performed statistical analyses and interpretation, and drafted the manuscript.

Junzhang Tian, Cheng Li, Wanmin Lian, Jingjun He, Hongying Qu, Xiaojie Wang, Hongmei Liu: provided professional and statistical support, and made several critical revisions to the manuscript.

All authors read and approved the final manuscript.

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Competing interests: None declared.

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Patient consent for publication: Not required.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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Tables and Figure legends:

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Table 3. Relationship between risk factors and risk of obesity in the models.

Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Figure 1. Location of Guangdong Second Provincial General Hospital (Guangzhou, Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.

Figure 2. Flow diagram showing selection process of participants in our study.

Supplemental data:

Supplementary Figure 1. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different times of medical checkups.

Supplementary Figure 2. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different years of medical checkups (from 2010 to 2018).

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Characteristics	All patients	Obesity[a]	Non-obesity	*p*-value[b]
	n=15959	n=1227	n=14732	
SUA (μmol/L) [SD]	367.05 (97.97)	434.95 (97.65)	361.32 (95.82)	<0.001
Age (years) [SD]	37.38 (13.27)	40.40 (13.40)	37.13 (13.23)	<0.001
Male [n, (%)]	10023 (62.8)	1012 (82.5)	9011 (61.2)	<0.001
SBP (mmHg) [SD]	121.09 (15.85)	131.78 (16.47)	120.19 (15.47)	<0.001
DBP (mmHg) [SD]	73.84 (10.31)	81.16 (11.41)	73.23 (9.97)	<0.001
TC (mmol/L) [SD]	4.88 (0.93)	5.19 (0.95)	4.86 (0.93)	<0.001
TG (mmol/L) [SD]	1.46 (1.10)	2.18 (1.49)	1.40 (1.04)	<0.001
HDL-c (mmol/L) [SD]	1.26 (0.25)	1.15 (0.22)	1.27 (0.25)	<0.001
LDL-c (mmol/L) [SD]	2.92 (0.78)	3.20 (0.80)	2.90 (0.77)	<0.001
FPG (mmol/L) [SD]	5.06 (1.04)	5.51 (1.61)	5.03 (0.97)	<0.001
BUN (mmol/L) [SD]	4.78 (1.25)	5.07 (1.30)	4.75 (1.24)	<0.001
CR (mmol/L) [SD]	94.57 (17.12)	100.05 (16.17)	94.11 (17.12)	<0.001

Note: Continuous variables are presented as the means (standard derivation); SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr, creatinine.

[a] Obesity was defined as body mass index (BMI) ≥28.0 kg/m^2.

[b] *p* value for the difference of variables between the two datasets based on independent sample t-test or chi-square test.

*The average number of health checkup for each participant is 2.62.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Variable	Obesity prevalence, n (%) [a]		
	Normal SUA	High SUA	P-value
Gender			
Male	357/5280 (6.8)	570/3768 (15.1)	<0.001
Female	104/4431 (2.3)	97/937 (10.3)	<0.001
Age group			
<30	88/3509 (2.5)	168/1643 (10.2)	<0.001
30-44	182/3736 (4.9)	309/1692 (18.3)	<0.001
45-59	121/1727 (7.0)	125/865 (14.5)	<0.001
60-74	54/606 (8.9)	53/378 (14.0)	<0.001
≥75	11/134 (8.2)	12/127 (9.4)	<0.001
Overall	456/9711 (4.6)	669/4705 (14.2)	<0.001

Note: High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

[a]Obesity prevalence = (n of obesity) / (total participants).

Table 3. Relationship between risk factors and risk of obesity in the models.

Variable	Model 1[c]		Model 2[d]	
	OR[a] *(95%CI*[b]*)*	*p*-value	*OR*[a] *(95%CI*[b]*)*	*p*-value
Continuous analysis				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.84 (1.77,1.90)	<0.001	1.85 (1.77,1.91)	<0.001
Gender [n, (%)]				
Female	Reference		Reference	
Male	1.27 (1.16,1.39)	<0.001	1.45 (1.32,1.60)	<0.001
Age (years)	1.02 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001
Categorical analysis				
SUA[e]				
Normal SUA	Reference		Reference	
High SUA	2.02 (1.84, 2.23)	<0.001	2.57 (2.31, 2.87)	<0.001
Gender				
Female	Reference		Reference	
Male	1.25 (1.09, 1.43)	0.002	1.69 (1.59, 1.79)	<0.001
Age group				
<30	Reference		Reference	
30-44	1.38 (1.14, 1.66)	0.001	1.73 (1.54, 1.91)	<0.001
45-59	1.07 (0.89, 1.30)	0.475	1.94 (1.72, 2.18)	<0.001
60-74	1.12 (0.90, 1.38)	0.314	1.99 (1.72, 2.32)	<0.001
≥75	0.95 (0.71, 1.27)	0.718	1.86(1.50, 2.31)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model 1 was adjusted for the variables of SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on the first time of medical checkup participants by using multivariate logistic regression model (LRM).

[d]Model 2 was adjusted for the variables of repeated times or years of medical checkup, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

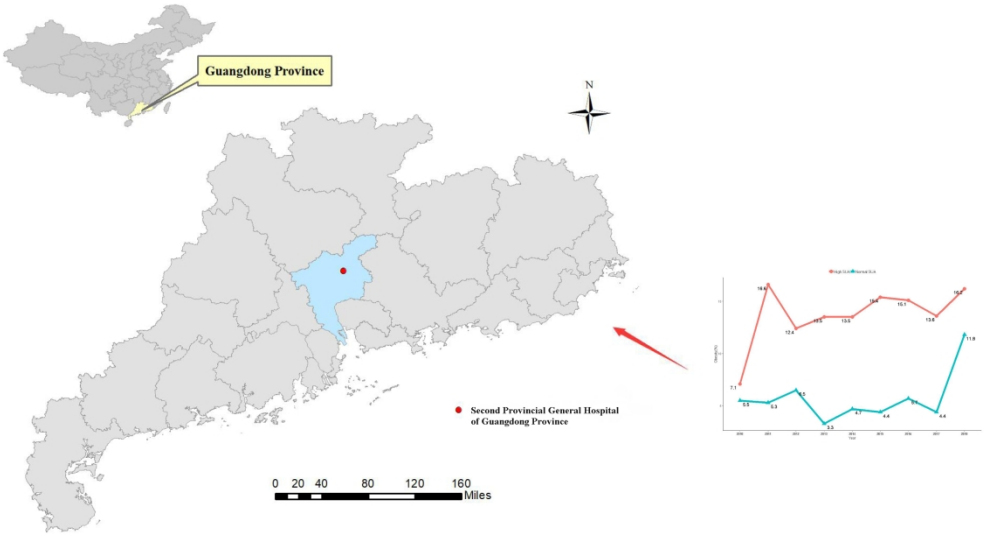
Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Variable	**Generalized estimation equation model (GEE)[c]**			
Gender	**Male**		**Female**	
	OR[a] (95%CI[b])	***p*-value**	***OR[a] (95%CI[b])***	***p*-value**
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.40 (2.23,2.59)	<0.001	3.79 (3.23,4.45)	<0.001
Age group	**Youth (<65 year)**		**Elderly (≥65 year)**	
	OR[a] (95%CI[b])	***p-value***	***OR[a] (95%CI[b])***	***p-value***
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.00 (1.00,1.01)	<0.001
Per-SD	1.87 (1.80,1.94)	<0.001	1.48 (1.34,1.62)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.78 (2.58,2.99)	<0.001	1.99 (1.63,2.43)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.



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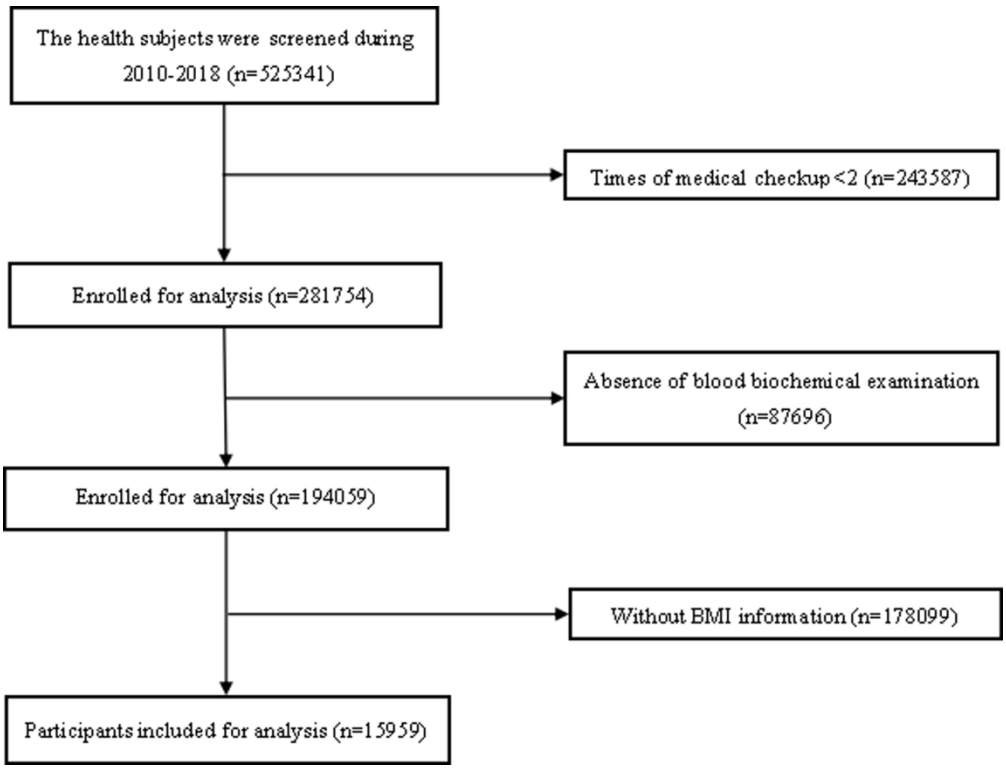

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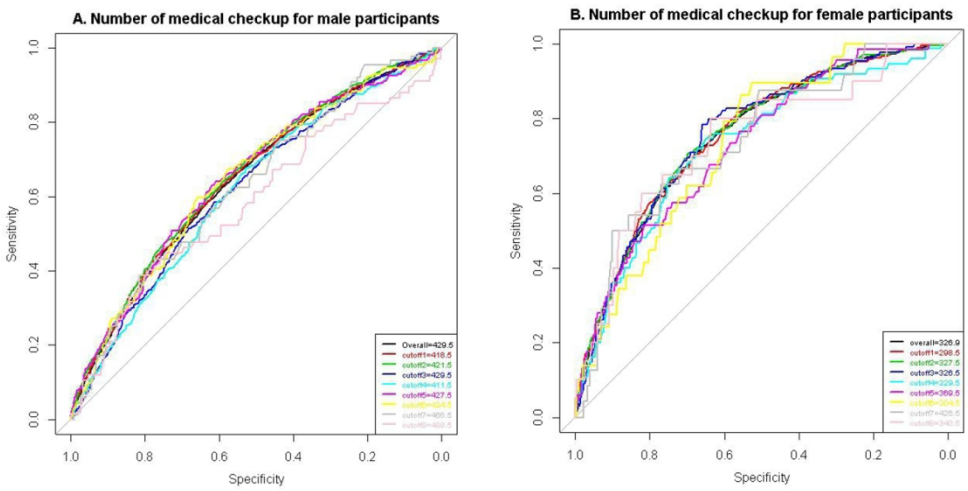

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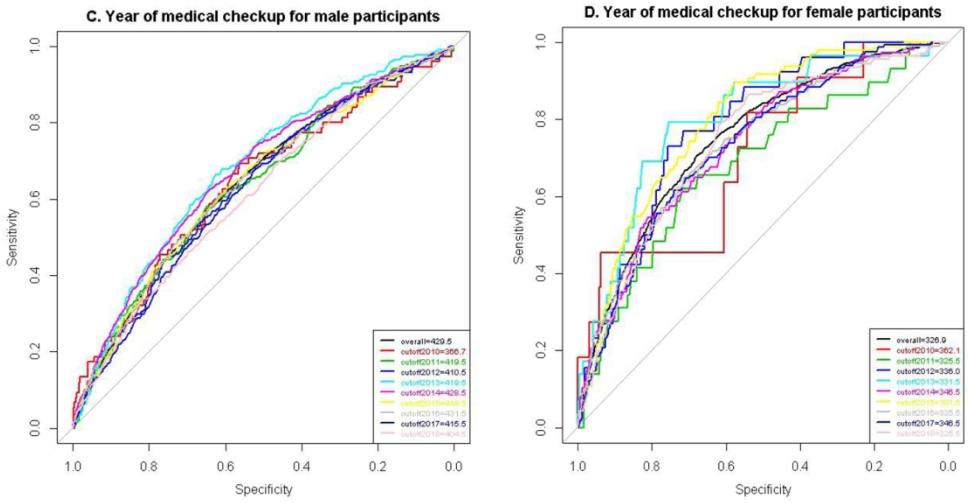

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	7-8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e*) Describe any sensitivity analyses	8-9

Continued on next page

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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	9-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
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	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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.

BMJ Open

Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Abstract

Objectives: Hyperuricemia has been reported to be significantly associated with risk of obesity. However, previous studies on the association between serum uric acid (SUA) and body mass index (BMI) yielded conflicting results. The present study examined the relationship between SUA and obesity among Chinese adults.

Methods: Data were collected at Guangdong Second Provincial General Hospital in Guangzhou City, China between January 2010 and December 2018. Participants with ≥2 medical checkup times were included in our analyses. Physical examinations and laboratory measurement variables were obtained from the medical checkup system. The high SUA level group was classified as participants with hyperuricemia, and obesity was defined as BMI≥28kg/m^2. Logistic regression model (LRM) was performed for data at baseline. For all participants, generalized estimation equation (GEE) model was used to assess the association between SUA and obesity, where the data were repeatedly measured over the nine-year study period. Subgroup analyses were performed by gender and age group. We calculated the cut-off values for SUA of obesity using the receiver operating characteristic curves (ROC) technique.

Results: A total of 15,959 participants (10,023 males and 5,936 females) were included in this study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic regression analysis at baseline, we observed a positive association between SUA and risk of obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95% CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male (OR=1.45) and elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant associations between SUA and obesity with higher risk in female (OR=2.35) and young

participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48). The SUA cut off points for risk of obesity using ROC curves were approximately consistent with the international standard.

Conclusions: Our study observed higher SUA level was associated with increased risk of obesity. More high-quality research is needed to further support these findings.

Keywords: serum uric acid, obesity, generalized estimation equation model, risk factors, China

Strengths and limitations of this study

- This is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China.
- The study analysis was based on the GEE model which can increase the accuracy of the prediction.
- The results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.
- The younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

Introduction

An individual's health behavior can influence both physical health and ability to recover from an illness. Annual medical checkup is an example of a positive health behavior, as this preventative measure is associated with earlier disease detection, greater treatment success, and faster recovery from a disease [1]. For this reason, medical data obtained from primary care is a useful source as it includes information on symptoms and healthcare utilization, all beneficial for use in prediction analysis. Medical checkup data often includes a variety of diagnostic tests to assess health status for early detection and disease prevention. Additionally, medical checkup data provides valuable information on present and past health conditions that are generally difficult to obtain in most population-based data [2]. More specifically, medical checkup data is a reliable and objective measure for identifying chronic diseases such as hyperuricemia and obesity.

Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting in hyperuricemia [3, 4]. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and 7.9% for women [5]. Additionally, in 2019 the obesity prevalence was nearing 12% in China. Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was reported to be independently correlated with changes in uric acid concentration, there might be an interaction between them as suggested in prior pathophysiological and metabolic studies [6]. Epidemiological and clinical evidence supports a strong significant positive association between SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq [7]. A cross-sectional study showed that body mass index (BMI) significantly increases with elevated SUA among 27,009 middle-aged and elderly Chinese adults [8]. Previous research showed that hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis [9]. With the increasing prevalence of obesity among adults with hyperuricemia, it is of public health importance to evaluate the long-term epidemiological transitions to develop policies centered on intervention.

Numerous trend analyses have reported the association between SUA and BMI based on short-term survey data in China [10, 11]. However, there remains a gap in evidence regarding the long-term trend for providing estimates on the risks of obesity among Chinese adults during the last two decades. Therefore, the present study aimed to examine the relationship between SUA and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

Methods

Study design and subjects

We conducted a large retrospective study in China. Medical examinations were performed in 2010 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical checkups; (2) absence of blood biochemical examination; and (3) no documented information on BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

Measurements

All participants were invited to join an in-person evaluation that included physical examination and laboratory testing. Physical examinations were conducted following a standardized protocol, including weight, height, waist circumference, hip circumference, and blood pressure. Waist circumference was measured around the midway between the lowest border of the ribs and iliac crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated measurements in the presence of researchers. Laboratory measurements were obtained to measure SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).

Outcomes and definitions

Hyperuricemia was defined as having SUA concentrations>7.0 mg/dL (416.4μmol/L) in men or>6.0 mg/dL (356.9μmol/L) in women [12, 13]. SUA levels were categorized into two groups (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The high SUA level group was classified as participants with hyperuricemia. BMI was defined as weight divided by height^2 (kg/m^2) and categorized into two groups (non-obese [< 28 kg/m^2] and obese [≥28kg/m^2]) based on the Asia-Pacific criteria set by the World Health Organization [14, 15]. We excluded patients taken drugs that might affect uric acid metabolism, such as losartan, furosemide, and allopurinol.

Statistical analysis

We conducted descriptive analysis to present the characteristics of baselines participants. Continuous variables were reported as mean ± standard derivation (SD) and categorical variables as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese and non-obese) were performed using Student' t-tests for continuous variables and Chi-square analyses for categorical variables. Logistic regression model (LRM) was used to evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also utilized generalized estimating equations (GEE) models with unstructured correlation structures to quantify their longitudinal association between SUA and risk of obesity [16], given the data on SUA and obesity were repeatedly measured over the 9-year study period. All models were adjusted for age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 μmol/L or per-SD increase in SUA.

We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age group (youth <65 years vs. elderly ≥65 years). Additionally, we calculated the cut-off values of SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria including (1) the point on the curve with minimum distance from the left-upper corner of the unit

square; and (2) the point where the Youden's index is maximum [17]. A two-sided p-value less than 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

There were no patient and/or public involvement in the design of this study.

Results

There were 15,959 participants (10,023 males) included in this study. The average number of health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD: 13.27) and a mean SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. There were 1,227 (7.6%) participants that were obese at baseline. Significant differences between the obese and non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR (p-value < 0.001) **(Table 1)**. In total, the prevalence of obesity was approximately 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The prevalence of obesity significantly increased with the number of medical checkup years in the group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078 participants developed obesity over the 9-year period.

As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for SUA [per-1 OR=1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.84 (95% CI: 1.77,1.90)], age [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic regression analysis (Model 1). When converted to categorical analysis, the risks of obesity were greater among those with high level of SUA, males and younger participants. Likewise, with

longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2), consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1 OR= 1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.85 (95% CI: 1.77,1.91)] for SUA, OR=1.45 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by categorical variables, we observed similar results with higher risk in male and elderly participants.

As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup analyses. Significant associations between SUA and risk of obesity were observed, where female [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an elevated risk. We also did the analysis of baseline uric acid values vs obesity at the 9-year mark in males and females, respectively where one eliminates baseline cases with hypertension, diabetes or elevated BS, dyslipidemia, normal kidney function, baseline obesity. This result was consistent with the subgroup analysis and well validate the data.

To calculate the discrimination ability of SUA among obese participants at different times of medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the overall cut-off values of SUA were 429.5μmol/L (range: 411.5-488.5 μmol/L) in males and 326.9μmol/L (range: 298.5-426.5 μmol/L) in females when stratified by different times of medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5 μmol/L (range: 366.7-431.5 μmol/L) in males and 326.9 μmol/L (range: 301.5-362.1 μmol/L) in females when stratified by different years of medical checkups.

Discussion

To the best of our knowledge, this is the first longitudinal study that estimated the relationship

between SUA and obesity over a long time period in China. The prevalence of obesity was approximately 14.2% for high SUA level. Previous studies found that the prevalence of hyperuricemia ranged from 2.5 to 25 % depending on the study population country [18]. For instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand [19, 20]. Overall, we found high SUA level was associated with increased risk of obesity, within OR value of 1.85 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies [21, 22]. Currently, obesity and hyperuricemia, as well as their associated health complications (e.g. metabolic syndrome) have emerged as a major public health concern as a result of the growing prevalence, and the estimated economic burden [7].

Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity, suggesting the influence of overproduction and poor renal excretion [23]. Prior studies reported that increased SUA level is closely related to excessive production of UA and the reduction of urinary uric acid excretion and clearance [24]. This ultimately leads to increased risk of patients with visceral fatty obesity [23]. Visceral fat accumulation (VFA) results in a large influx of plasma free fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and subsequently produced large amounts of UA through the activated UA synthesis pathway [25, 26]. Additionally, many researchers have reported a significant correlation between VFA and BMI [27, 28]. Therefore, because of the close biological relationship between UA and BMI, it is of great importance for preventive medicine to pay attention to the interaction between UA and BMI.

Conflicting results regarding gender and age differences for the association between SUA and obesity have been reported [10, 29]. Our study found significant differences in obesity participants with elevated OR value among high SUA level, male, and elderly for all medical checkup participants. A similar study reported a positive relationship between BMI and SUA levels among healthy individuals in China [30]. Nevertheless, in this study the subgroup analyses showed that significant associated risk between SUA and obesity were observed higher in female and young

participants. This is consistent with a Thailand study that reported high SUA concentrations were associated with greater risk of obesity in females [31]. However, study in Bangladesh and Japan reported that elevated SUA predicted obesity higher in males and the elderly[8, 29, 31]. Perhaps the associations of SUA with obesity varies by populations. Moreover, in a 10-year follow-up study, BMI was observed to significantly increase with higher SUA levels regardless of race and gender [32]. Therefore, greater attention should be provided to those vulnerable populations in clinical guidelines.

An important observation was that association between SUA and risk of obesity in the LRM [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE model [OR= (1.85 (1.77,1.91)] for 9-year all participants. The risk of obesity within hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can reflect the development of chronic diseases [33]. Regarding the assessment of cut-off values from ROC of SUA in obesity participants, the cut-off values of SUA were 429.5μmol/L in males and 326.9μmol/L in females in stratified analysis by times or years of medical checkup. The cut-off value was approximately consistent with the international standard for males [34]. However, it was underestimated for women in the group of obese participants. Perhaps the proportion of females were fewer in this study. The cut-off values for SUA in the study may be useful for distinguishing tests among obesity and non-obesity participants, which were significant for certain risk value prediction and guidance[35].

We must note several limitations in the present study. First, the underlying mechanism by which SUA is increased in obese individuals remains not well understood. Second, this study did not collect information on whether participants were prescribed medication to treat hyperuricemia. Additionally, some medications used to treat hypertension may increase uric acid levels. Third, there are numerous confounding factors that have not been considered, which can be studied together with questionnaires in the future. Moreover, the younger screening population in this

study may underestimate the increased risk of uric acid among the elderly obese.

The present study has several strengths that must be noted. First, to our knowledge this is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China. Second, the study analysis was based on the GEE model with high quality data by controlling for confounding factors, which can increase the accuracy of the prediction. Third, participants were representative of the general population with regard to clinical checkup and obesity status, enhancing the generalizability of our findings. Moreover, results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.

This study filled current gaps in literature by analyzing the relationship between SUA and obesity using medical checkup data. We observed that medical checkup data can be used to improve the risk of obesity prediction accuracy. The medical checkup data used in this study can help provide information that will facilitate intervention development and adoption at the individual level [36]. The utility of medical checkup data can potentially reach beyond predictive power alone in the near future.

Conclusions

In conclusion, our study observed significant associations between SUA and obesity in this 9-year longitudinal study. We mainly found higher SUA level was associated with increased risk of obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the number of medical checkup years in the group with high level of SUA. Additionally, the increased risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses revealed significant associations between SUA and obesity with higher risk for females and young participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent

with the international standard. More evidence from well-designed studies are needed to confirm our findings.

Author Contributions:

Guowei Li, Jie Zeng, Guanming Li: conceived and designed the study.

Guowei Li, Jie Zeng, Wayne R. Lawrence, Jun Yang: acquired data, performed statistical analyses and interpretation, and drafted the manuscript.

Junzhang Tian, Cheng Li, Wanmin Lian, Jingjun He, Hongying Qu, Xiaojie Wang, Hongmei Liu: provided professional and statistical support, and made several critical revisions to the manuscript.

All authors read and approved the final manuscript.

Acknowledgments:

None declared.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

Data availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information.

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Tables and Figure legends:

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Table 3. Relationship between risk factors and risk of obesity in the models.

Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Figure 1. Location of Guangdong Second Provincial General Hospital (Guangzhou, Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.

Figure 2. Flow diagram showing selection process of participants in our study.

Supplemental data:

Supplementary Figure 1. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different times of medical checkups.

Supplementary Figure 2. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different years of medical checkups (from 2010 to 2018).

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Characteristics	All patients	Obesity[a]	Non-obesity	*p*-value[b]
	n=15959	n=1227	n=14732	
SUA (μmol/L) [SD]	367.05 (97.97)	434.95 (97.65)	361.32 (95.82)	<0.001
Age (years) [SD]	37.38 (13.27)	40.40 (13.40)	37.13 (13.23)	<0.001
Male [n, (%)]	10023 (62.8)	1012 (82.5)	9011 (61.2)	<0.001
SBP (mmHg) [SD]	121.09 (15.85)	131.78 (16.47)	120.19 (15.47)	<0.001
DBP (mmHg) [SD]	73.84 (10.31)	81.16 (11.41)	73.23 (9.97)	<0.001
TC (mmol/L) [SD]	4.88 (0.93)	5.19 (0.95)	4.86 (0.93)	<0.001
TG (mmol/L) [SD]	1.46 (1.10)	2.18 (1.49)	1.40 (1.04)	<0.001
HDL-c (mmol/L) [SD]	1.26 (0.25)	1.15 (0.22)	1.27 (0.25)	<0.001
LDL-c (mmol/L) [SD]	2.92 (0.78)	3.20 (0.80)	2.90 (0.77)	<0.001
FPG (mmol/L) [SD]	5.06 (1.04)	5.51 (1.61)	5.03 (0.97)	<0.001
BUN (mmol/L) [SD]	4.78 (1.25)	5.07 (1.30)	4.75 (1.24)	<0.001
CR (mmol/L) [SD]	94.57 (17.12)	100.05 (16.17)	94.11 (17.12)	<0.001

Note: Continuous variables are presented as the means (standard derivation); SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr, creatinine.

[a] Obesity was defined as body mass index (BMI) ≥28.0 kg/m^2.

[b] *p* value for the difference of variables between the two datasets based on independent sample t-test or chi-square test.

*The average number of health checkup for each participant is 2.62.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Variable	Obesity prevalence, n (%) [a]		
	Normal SUA	High SUA	P-value
Gender			
Male	357/5280 (6.8)	570/3768 (15.1)	<0.001
Female	104/4431 (2.3)	97/937 (10.3)	<0.001
Age group			
<30	88/3509 (2.5)	168/1643 (10.2)	<0.001
30-44	182/3736 (4.9)	309/1692 (18.3)	<0.001
45-59	121/1727 (7.0)	125/865 (14.5)	<0.001
60-74	54/606 (8.9)	53/378 (14.0)	<0.001
≥75	11/134 (8.2)	12/127 (9.4)	<0.001
Overall	456/9711 (4.6)	669/4705 (14.2)	<0.001

Note: High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

[a]Obesity prevalence = (n of obesity) / (total participants).

Table 3. Relationship between risk factors and risk of obesity in the models.

Variable	Model 1[c]		Model 2[d]	
	OR[a] *(95%CI*[b]*)*	*p*-value	*OR*[a] *(95%CI*[b]*)*	*p*-value
Continuous analysis				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.84 (1.77,1.90)	<0.001	1.85 (1.77,1.91)	<0.001
Gender [n, (%)]				
Female	Reference		Reference	
Male	1.27 (1.16,1.39)	<0.001	1.45 (1.32,1.60)	<0.001
Age (years)	1.02 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001
Categorical analysis				
SUA[e]				
Normal SUA	Reference		Reference	
High SUA	2.02 (1.84, 2.23)	<0.001	2.57 (2.31, 2.87)	<0.001
Gender				
Female	Reference		Reference	
Male	1.25 (1.09, 1.43)	0.002	1.69 (1.59, 1.79)	<0.001
Age group				
<30	Reference		Reference	
30-44	1.38 (1.14, 1.66)	0.001	1.73 (1.54, 1.91)	<0.001
45-59	1.07 (0.89, 1.30)	0.475	1.94 (1.72, 2.18)	<0.001
60-74	1.12 (0.90, 1.38)	0.314	1.99 (1.72, 2.32)	<0.001
≥75	0.95 (0.71, 1.27)	0.718	1.86(1.50, 2.31)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model 1 was adjusted for the variables of SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on the first time of medical checkup participants by using multivariate logistic regression model (LRM).

[d]Model 2 was adjusted for the variables of repeated times or years of medical checkup, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

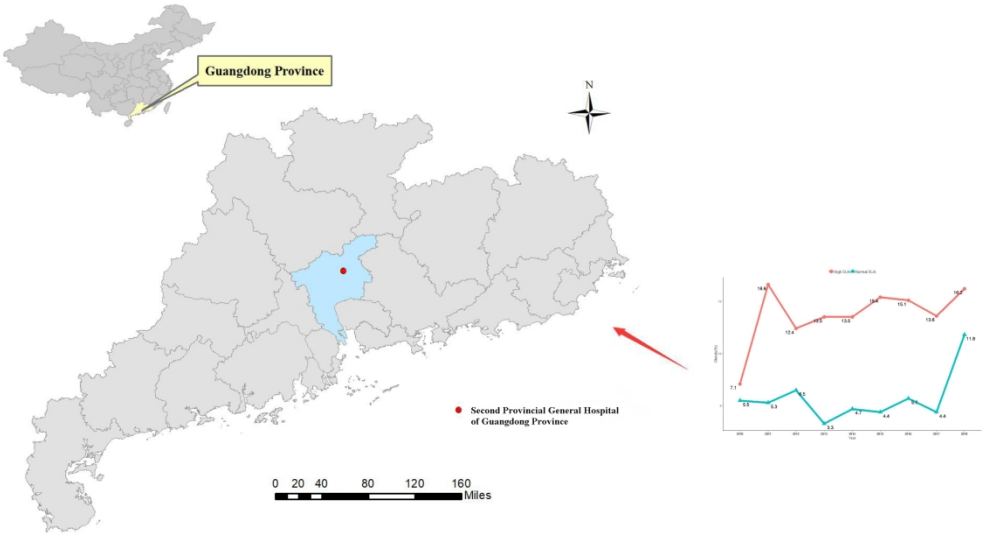
Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Variable	**Generalized estimation equation model (GEE)[c]**			
Gender	**Male**		**Female**	
	OR[a] (95%CI[b])	***p*-value**	***OR[a] (95%CI[b])***	***p*-value**
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.40 (2.23,2.59)	<0.001	3.79 (3.23,4.45)	<0.001
Age group	**Youth (<65 year)**		**Elderly (≥65 year)**	
	OR[a] (95%CI[b])	***p-value***	***OR[a] (95%CI[b])***	***p-value***
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.00 (1.00,1.01)	<0.001
Per-SD	1.87 (1.80,1.94)	<0.001	1.48 (1.34,1.62)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.78 (2.58,2.99)	<0.001	1.99 (1.63,2.43)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.



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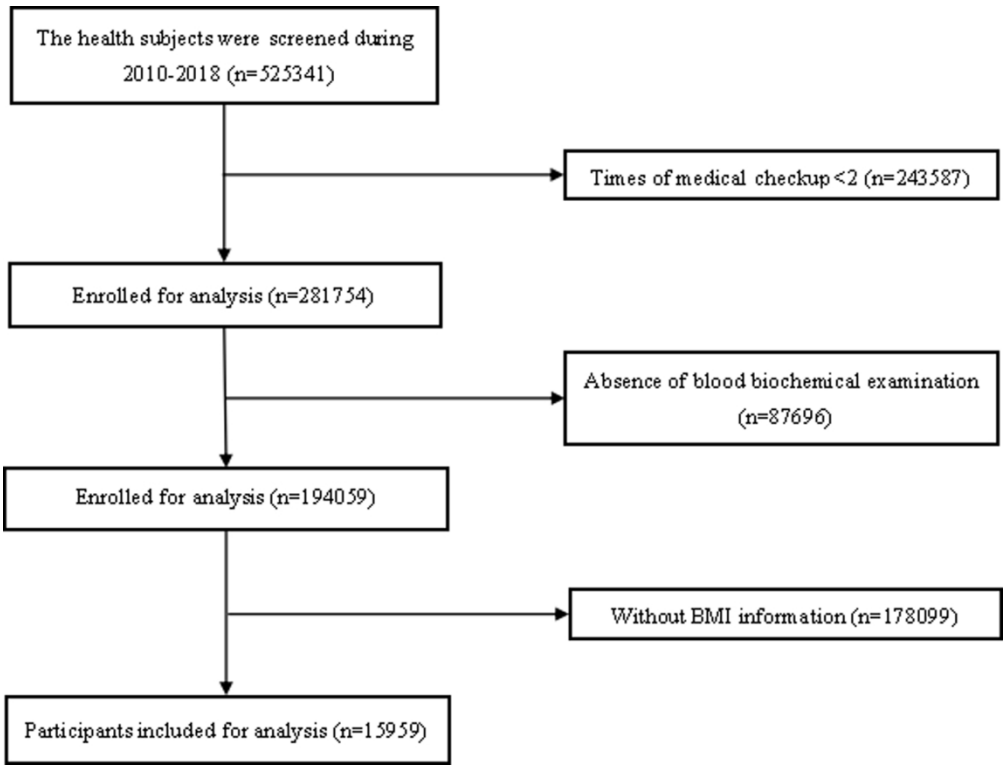

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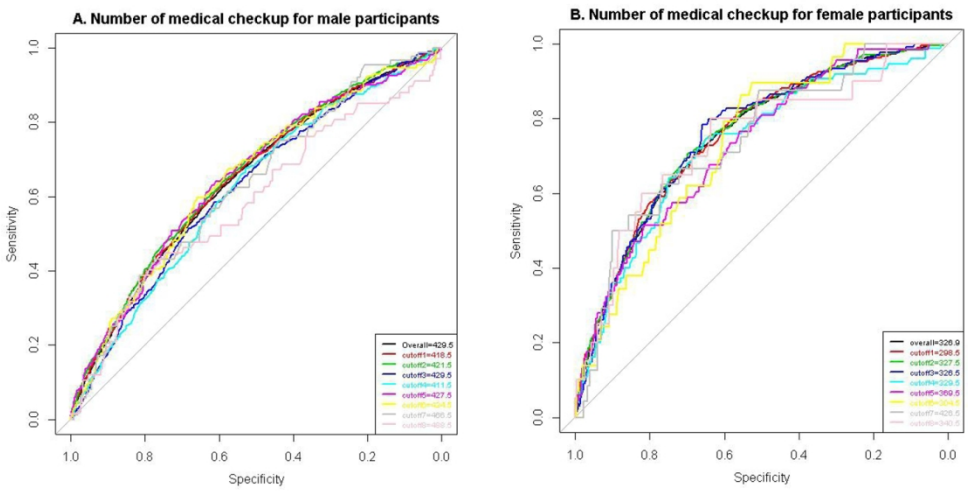

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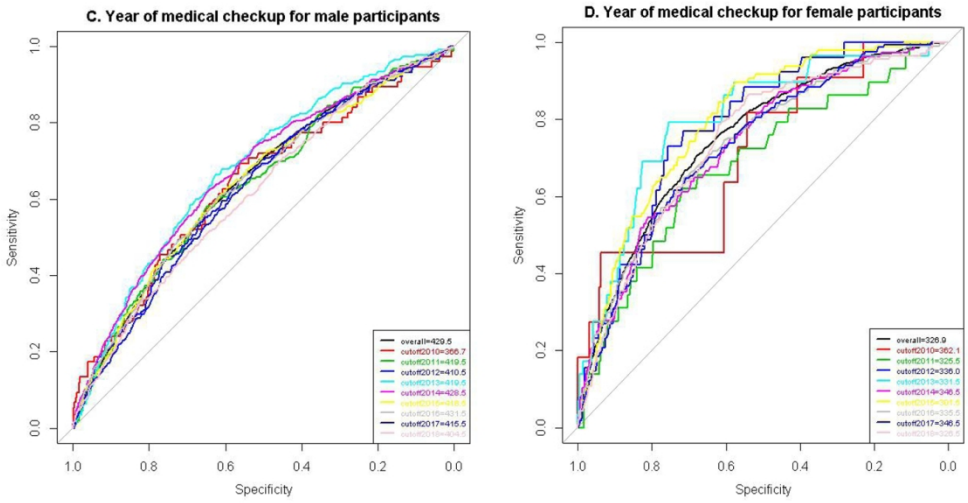

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	7-8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e*) Describe any sensitivity analyses	8-9

Continued on next page

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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	9-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
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	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Abstract

Objectives: Hyperuricemia has been reported to be significantly associated with risk of obesity. However, previous studies on the association between serum uric acid (SUA) and body mass index (BMI) yielded conflicting results. The present study examined the relationship between SUA and obesity among Chinese adults.

Methods: Data were collected at Guangdong Second Provincial General Hospital in Guangzhou City, China between January 2010 and December 2018. Participants with ≥2 medical checkup times were included in our analyses. Physical examinations and laboratory measurement variables were obtained from the medical checkup system. The high SUA level group was classified as participants with hyperuricemia, and obesity was defined as BMI≥28kg/m^2. Logistic regression model (LRM) was performed for data at baseline. For all participants, generalized estimation equation (GEE) model was used to assess the association between SUA and obesity, where the data were repeatedly measured over the nine-year study period. Subgroup analyses were performed by gender and age group. We calculated the cut-off values for SUA of obesity using the receiver operating characteristic curves (ROC) technique.

Results: A total of 15,959 participants (10,023 males and 5,936females) were included in this study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic regression analysis at baseline, we observed a positive association between SUA and risk of obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95% CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male (OR=1.45) and elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant associations between SUA and obesity with higher risk in female (OR=2.35) and young

participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48). The SUA cutoff points for risk of obesity using ROC curves were approximately consistent with the international standard.

Conclusions: Our study observed higher SUA level was associated with increased risk of obesity. More high-quality research is needed to further support these findings.

Keywords: serum uric acid, obesity, generalized estimation equation model, risk factors, China

Strengths and limitations of this study

- This is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China.
- The study analysis was based on the GEE model which can increase the accuracy of the prediction.
- The results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.
- The younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

Introduction

An individual's health behavior can influence both physical health and ability to recover from an illness. Annual medical checkup is an example of a positive health behavior, as this preventative measure is associated with earlier disease detection, greater treatment success, and faster recovery from a disease [1]. For this reason, medical data obtained from primary care is a useful source as it includes information on symptoms and health care utilization, all beneficial for use in prediction analysis. Medical checkup data often includes a variety of diagnostic tests to assess health status for early detection and disease prevention. Additionally, medical checkup data provides valuable information on present and past health conditions that are generally difficult to obtain in most population-based data [2].More specifically, medical checkup data is a reliable and objective measure for identifying chronic diseases such as hyperuricemia and obesity.

Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting in hyperuricemia[3, 4]. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and 7.9% for women[5]. Additionally, in 2019 the obesity prevalence was nearing 12% in China. Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was reported to be independently correlated with changes in uric acid concentration, there might be an interaction between them as suggested in prior pathophysiological and metabolic studies [6]. Epidemiological and clinical evidence supports a strong significant positive association between SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq [7]. A cross-sectional study showed that body mass index (BMI) significantly increases with elevated SUA among 27,009 middle-aged and elderly Chinese adults [8]. Previous research showed that hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis[9]. With the increasing prevalence of obesity among adults with hyperuricemia, it is of public health importance to evaluate the long-term epidemiological transitions to develop policies centered on intervention.

Numerous trend analyses have reported the association between SUA and BMI based on short-term survey data in China[10, 11]. However, there remains a gap in evidence regarding the long-term trend for providing estimates on the risks of obesity among Chinese adults during the last two decades. Therefore, the present study aimed to examine the relationship between SUA and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

Methods

Study design and subjects

We conducted a large retrospective study in China. Medical examinations were performed in 2010 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical checkups; (2) absence of blood biochemical examination; and (3) no documented information on BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

Measurements

All participants were invited to join an in-person evaluation that included physical examination and laboratory testing. Physical examinations were conducted following a standardized protocol, including weight, height, waist circumference, hip circumference, and blood pressure. Waist circumference was measured around the midway between the lowest border of the ribs and iliac crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated measurements in the presence of researchers. Laboratory measurements were obtained to measure SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).

Outcomes and definitions

Hyperuricemia was defined as having SUA concentrations>7.0 mg/dL (416.4μmol/L) in men or>6.0 mg/dL (356.9μmol/L) in women[12, 13]. SUA levels were categorized into two groups (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The high SUA level group was classified as participants with hyperuricemia. BMI was defined as weight divided by height^2 (kg/m^2) and categorized into two groups (non-obese [< 28 kg/m^2] and obese [≥28kg/m^2]) based on the Asia-Pacific criteria set by the World Health Organization [14, 15]. We excluded patients taken drugs that might affect uric acid metabolism, such as losartan, furosemide, and allopurinol.

Statistical analysis

We conducted descriptive analysis to present the characteristics of baselines participants. Continuous variables were reported as mean ± standard derivation (SD) and categorical variables as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese and non-obese) were performed using Student' t-tests for continuous variables and Chi-square analyses for categorical variables. Logistic regression model (LRM) was used to evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also utilized generalized estimating equations (GEE) models with unstructured correlation structures to quantify their longitudinal association between SUA and risk of obesity [16], given the data on SUA and obesity were repeatedly measured over the 9-year study period. All models were adjusted for age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 μmol/L or per-SD increase in SUA.

We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age group (youth<65 years vs. elderly ≥65 years). Additionally, we calculated the cut-off values of SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria

including (1) the point on the curve with minimum distance from the left-upper corner of the unit square; and (2) the point where the Youden's index is maximum[17]. A two-sided p-valueless than 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

There were no patient and/or public involvement in the design of this study.

Results

There were 15,959 participants (10,023 males) included in this study. The average number of health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD: 13.27) and a mean SUA of 367.05μmol/L (SD: 97.97) at baseline, respectively. There were 1,227 (7.6%) participants that were obese at baseline. Significant differences between the obese and non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR (p-value < 0.001) **(Table 1)**. In total, the prevalence of obesity was approximately 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The prevalence of obesity significantly increased with the number of medical checkup years in the group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078 participants developed obesity over the 9-year period.

As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for SUA [per-1OR=1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.84 (95% CI: 1.77,1.90)], age [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic regression analysis (Model 1). When converted to categorical analysis, the risks of obesity were

greater among those with high level of SUA, males and younger participants. Likewise, with longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2), consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1 OR= 1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.85 (95% CI: 1.77,1.91)] for SUA, OR=1.45 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by categorical variables, we observed similar results with higher risk in male and elderly participants.

As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup analyses. Significant associations between SUA and risk of obesity were observed, where female [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an elevated risk. We also did the analysis of baseline uric acid values vs obesity at the 9-year mark in males and females, respectively where one eliminates baseline cases with hypertension, diabetes or elevated BS, dyslipidemia, normal kidney function, baseline obesity. This result was consistent with the subgroup analysis and well validate the data.

To calculate the discrimination ability of SUA among obese participants at different times of medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the overall cut-off values of SUA were 429.5μmol/L (range: 411.5-488.5 μmol/L) in males and326.9μmol/L (range: 298.5-426.5 μmol/L) in females when stratified by different times of medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5 μmol/L (range: 366.7-431.5 μmol/L) in males and 326.9 μmol/L (range: 301.5-362.1 μmol/L) in females when stratified by different years of medical checkups.

Discussion

To the best of our knowledge, this is the first longitudinal study that estimated the relationship between SUA and obesity over a long time period in China. The prevalence of obesity was approximately 14.2% for high SUA level. Previous studies found that the prevalence of hyperuricemia ranged from 2.5 to 25 % depending on the study population country [18].For instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand[19, 20]. Overall, we found high SUA level was associated with increased risk of obesity, within OR value of 1.85 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies [21, 22]. Currently, obesity and hyperuricemia, as well as their associated health complications (e.g. metabolic syndrome) have emerged as a major public health concern as a result of the growing prevalence, and the estimated economic burden[7].

Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity, suggesting the influence of overproduction and poor renal excretion[23]. Prior studies reported that increased SUA level is closely related to excessive production of UA and the reduction of urinary uric acid excretion and clearance [24]. This ultimately leads to increased risk of patients with visceral fatty obesity[23]. Visceral fat accumulation (VFA) results in a large influx of plasma free fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and subsequently produced large amounts of UA through the activated UA synthesis pathway[25, 26]. Additionally, many researchers have reported a significant correlation between VFA and BMI[27, 28]. Therefore, because of the close biological relationship between UA and BMI, it is of great importance for preventive medicine to pay attention to the interaction between UA and BMI.

Conflicting results regarding gender and age differences for the association between SUA and obesity have been reported[10, 29].Our study found significant differences in obesity participants with elevated OR value among high SUA level, male, and elderly for all medical checkup participants. A similar study reported a positive relationship between BMI and SUA levels among healthy individuals in China[30]. Nevertheless, in this study the subgroup analyses showed that significant

associated risk between SUA and obesity were observed higher in female and young participants. This is consistent with a Thailand study that reported high SUA concentrations were associated with greater risk of obesity in females[31]. However, study in Bangladesh and Japan reported that elevated SUA predicted obesity higher in males and the elderly[8, 29, 31]. Perhaps the associations of SUA with obesity varies by populations. Moreover, in a 10-year follow-up study, BMI was observed to significantly increase with higher SUA levels regardless of race and gender [32]. Therefore, greater attention should be provided to those vulnerable populations in clinical guidelines.

An important observation was that association between SUA and risk of obesity in the LRM [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE model [OR= (1.85 (1.77,1.91)] for 9-year all participants. The risk of obesity within hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can reflect the development of chronic diseases[33]. Regarding the assessment of cut-off values from ROC of SUA in obesity participants, the cut-off values of SUA were 429.5μmol/L in malesand326.9μmol/L in females in stratified analysis by times or years of medical checkup. The cut-off value was approximately consistent with the international standard for males[34]. However, it was underestimated for women in the group of obese participants. Perhaps the proportion of females were fewer in this study. The cut-off values for SUA in the study may be useful for distinguishing tests among obesity and non-obesity participants, which were significant for certain risk value prediction and guidance[35].

To our knowledge, we must note several limitations in the present study. First, the underlying mechanism by which SUA is increased in obese individuals remains not well understood. Second, this study did not collect information on whether participants were prescribed medication to treat hyperuricemia. Additionally, some medications used to treat hypertension may increase uric acid levels. Third, there are numerous confounding factors that have not been considered, which can be

studied together with questionnaires in the future. Moreover, the younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

The present study has several strengths that must be noted. First, to our knowledge this is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China. Second, the study analysis was based on the GEE model with high quality data by controlling for confounding factors, which can increase the accuracy of the prediction. Third, participants were representative of the general population with regard to clinical checkup and obesity status, enhancing the generalizability of our findings. Moreover, results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.

This study filled current gaps in literature by analyzing the relationship between SUA and obesity using medical checkup data. We observed that medical checkup data can be used to improve the risk of obesity prediction accuracy. The medical checkup data used in this study can help provide information that will facilitate intervention development and adoption at the individual level [36]. The utility of medical checkup data can potentially reach beyond predictive power alone in the near future.

Conclusions

In conclusion, our study observed significant associations between SUA and obesity in this 9-year longitudinal study. We mainly found higher SUA level was associated with increased risk of obesity. The prevalence of obesity was approximately 14.2%and significantly increased with the number of medical checkup years in the group with high level of SUA. Additionally, the increased risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses revealed significant associations between SUA and obesity with higher risk for females and young

participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent with the international standard. More evidence from well-designed studies are needed to confirm our findings.

Author Contributions:

Guowei Li, Jie Zeng,Guanming Li: conceived and designed the study.

Guowei Li, Jie Zeng, Wayne R. Lawrence, Jun Yang: acquired data, performed statistical analyses and interpretation, and drafted the manuscript.

Junzhang Tian, Cheng Li, Wanmin Lian, Jingjun He, Hongying Qu, Xiaojie Wang, Hongmei Liu: provided professional and statistical support, and made several critical revisions to the manuscript.

All authors read and approved the final manuscript.

Acknowledgments:

None declared.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

Ethics approval:

The need for consent was waived due to the nature of this study. The IRB waived the informed consent.

Data availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information.

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Tables and Figure legends:

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Table3. Relationship between risk factors and risk of obesity in the models.

Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Figure 1. Location of Guangdong Second Provincial General Hospital (Guangzhou, Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.

Figure 2. Flow diagram showing selection process of participants in our study.

Supplemental data:

Supplementary Figure1. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different times of medical checkups.

Supplementary Figure2. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different years of medical checkups (from 2010 to 2018).

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Characteristics	All patients	Obesity[a]	Non-obesity	*p*-value[b]
	n=15959	n=1227	n=14732	
SUA (μmol/L) [SD]	367.05 (97.97)	434.95 (97.65)	361.32 (95.82)	<0.001
Age (years) [SD]	37.38 (13.27)	40.40 (13.40)	37.13 (13.23)	<0.001
Male [n, (%)]	10023 (62.8)	1012 (82.5)	9011 (61.2)	<0.001
SBP (mmHg) [SD]	121.09 (15.85)	131.78 (16.47)	120.19 (15.47)	<0.001
DBP (mmHg) [SD]	73.84 (10.31)	81.16 (11.41)	73.23 (9.97)	<0.001
TC (mmol/L) [SD]	4.88 (0.93)	5.19 (0.95)	4.86 (0.93)	<0.001
TG (mmol/L) [SD]	1.46 (1.10)	2.18 (1.49)	1.40 (1.04)	<0.001
HDL-c (mmol/L) [SD]	1.26 (0.25)	1.15 (0.22)	1.27 (0.25)	<0.001
LDL-c (mmol/L) [SD]	2.92 (0.78)	3.20 (0.80)	2.90 (0.77)	<0.001
FPG (mmol/L) [SD]	5.06 (1.04)	5.51 (1.61)	5.03 (0.97)	<0.001
BUN (mmol/L) [SD]	4.78 (1.25)	5.07 (1.30)	4.75 (1.24)	<0.001
CR (mmol/L) [SD]	94.57 (17.12)	100.05 (16.17)	94.11 (17.12)	<0.001

Note: Continuous variables are presented as the means (standard derivation); SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr, creatinine.

[a] Obesity was defined as body mass index (BMI) ≥28.0 kg/m^2.

[b] *p* value for the difference of variables between the two data sets based on independent sample t-test or chi-square test.

*The average number of health checkup for each participant is 2.62.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Variable	Obesity prevalence, n (%) [a]		
	Normal SUA	High SUA	P-value
Gender			
Male	357/5280 (6.8)	570/3768 (15.1)	<0.001
Female	104/4431 (2.3)	97/937 (10.3)	<0.001
Age group			
<30	88/3509 (2.5)	168/1643 (10.2)	<0.001
30-44	182/3736 (4.9)	309/1692 (18.3)	<0.001
45-59	121/1727 (7.0)	125/865 (14.5)	<0.001
60-74	54/606 (8.9)	53/378 (14.0)	<0.001
≥75	11/134 (8.2)	12/127 (9.4)	<0.001
Overall	456/9711 (4.6)	669/4705 (14.2)	<0.001

Note: High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

[a]Obesity prevalence = (n of obesity) / (total participants).

Table 3. Relationship between risk factors and risk of obesity in the models.

Variable	Model 1[c]		Model 2[d]	
	OR[a] (95%CI[b])	*p*-value	*OR[a] (95%CI[b])*	*p*-value
Continuous analysis				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.84 (1.77,1.90)	<0.001	1.85 (1.77,1.91)	<0.001
Gender [n, (%)]				
Female	Reference		Reference	
Male	1.27 (1.16,1.39)	<0.001	1.45 (1.32,1.60)	<0.001
Age (years)	1.02 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001
Categorical analysis				
SUA[e]				
Normal SUA	Reference		Reference	
High SUA	2.02 (1.84, 2.23)	<0.001	2.57 (2.31, 2.87)	<0.001
Gender				
Female	Reference		Reference	
Male	1.25 (1.09, 1.43)	0.002	1.69 (1.59, 1.79)	<0.001
Age group				
<30	Reference		Reference	
30-44	1.38 (1.14, 1.66)	0.001	1.73 (1.54, 1.91)	<0.001
45-59	1.07 (0.89, 1.30)	0.475	1.94 (1.72, 2.18)	<0.001
60-74	1.12 (0.90, 1.38)	0.314	1.99 (1.72, 2.32)	<0.001
≥75	0.95 (0.71, 1.27)	0.718	1.86(1.50, 2.31)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model 1 was adjusted for the variables of SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on the first time of medical checkup participants by using multivariate logistic regression model (LRM).

[d]Model 2 was adjusted for the variables of repeated times or years of medical checkup, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

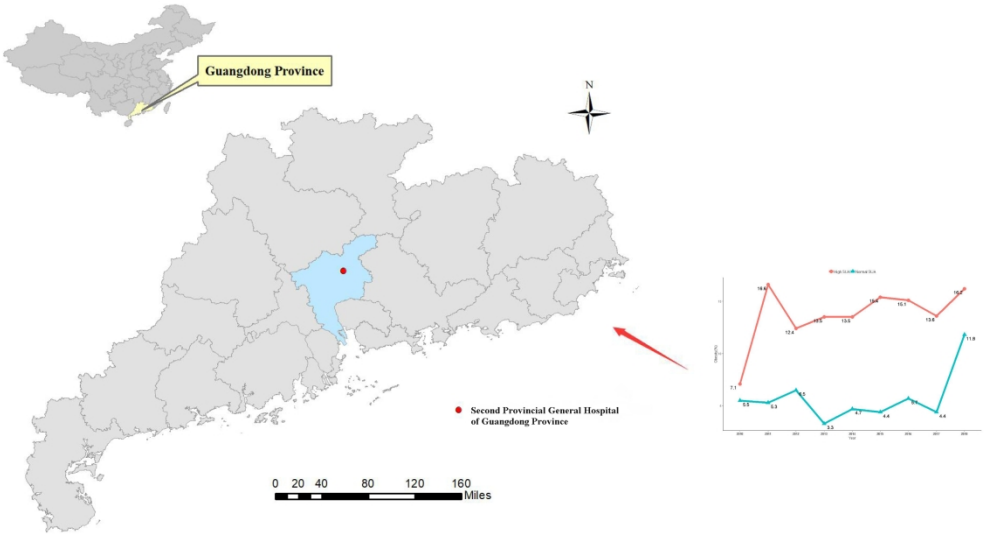
Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Variable	Generalized estimation equation model (GEE)[c]			
Gender	**Male**		**Female**	
	OR[a] (95%CI[b])	***p*-value**	***OR[a] (95%CI[b])***	***p*-value**
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.40 (2.23,2.59)	<0.001	3.79 (3.23,4.45)	<0.001
Age group	**Youth (<65 year)**		**Elderly (≥65 year)**	
	OR[a] (95%CI[b])	***p-value***	***OR[a] (95%CI[b])***	***p-value***
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.00 (1.00,1.01)	<0.001
Per-SD	1.87 (1.80,1.94)	<0.001	1.48 (1.34,1.62)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.78 (2.58,2.99)	<0.001	1.99 (1.63,2.43)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.



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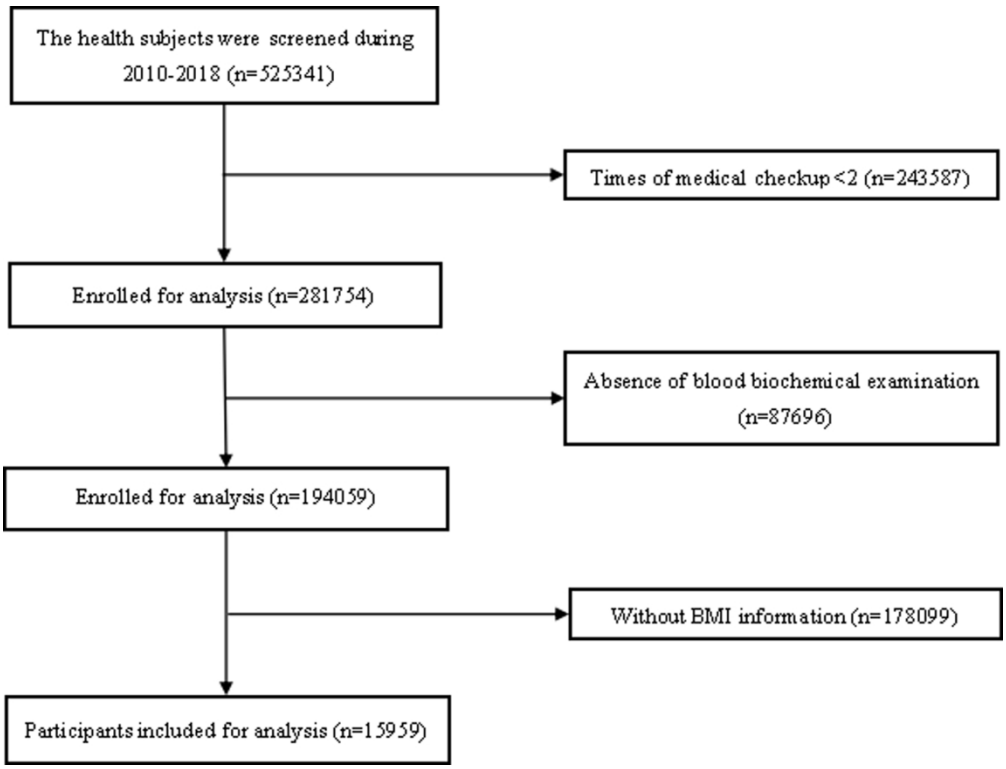

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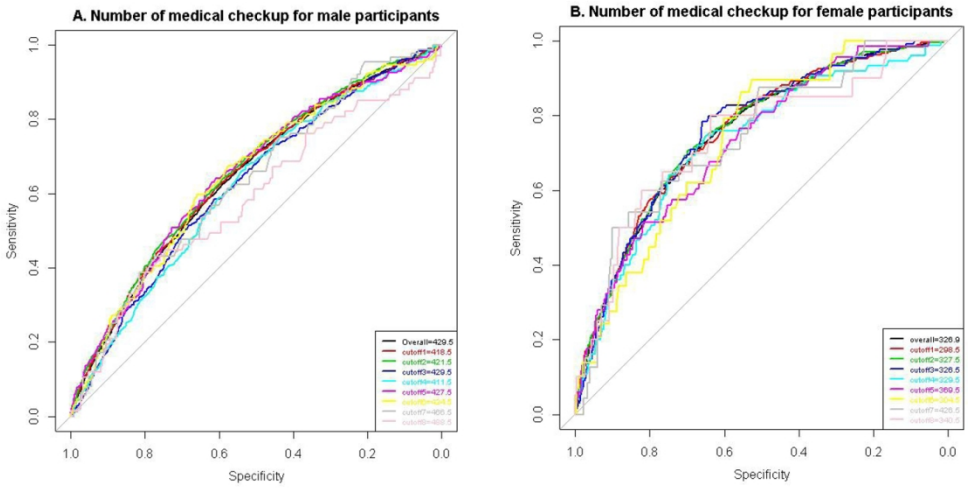

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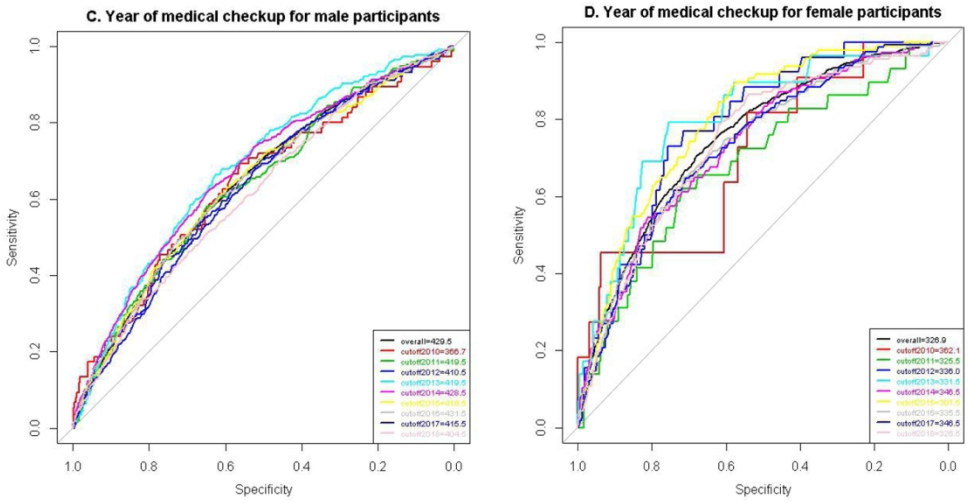

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	7-8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e*) Describe any sensitivity analyses	8-9

Continued on next page

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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	9-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
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	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Association between serum uric acid and obesity in Chinese adults: A nine-year longitudinal data analysis

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Abstract

Objectives: Hyperuricemia has been reported to be significantly associated with risk of obesity. However, previous studies on the association between serum uric acid (SUA) and body mass index (BMI) yielded conflicting results. The present study examined the relationship between SUA and obesity among Chinese adults.

Methods: Data were collected at Guangdong Second Provincial General Hospital in Guangzhou City, China between January 2010 and December 2018. Participants with ≥2 medical checkup times were included in our analyses. Physical examinations and laboratory measurement variables were obtained from the medical checkup system. The high SUA level group was classified as participants with hyperuricemia, and obesity was defined as BMI≥28kg/m^2. Logistic regression model (LRM) was performed for data at baseline. For all participants, generalized estimation equation (GEE) model was used to assess the association between SUA and obesity, where the data were repeatedly measured over the nine-year study period. Subgroup analyses were performed by gender and age group. We calculated the cut-off values for SUA of obesity using the receiver operating characteristic curves (ROC) technique.

Results: A total of 15,959 participants (10,023 males and 5,936females) were included in this study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic regression analysis at baseline, we observed a positive association between SUA and risk of obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95% CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male (OR=1.45) and elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant associations between SUA and obesity with higher risk in female (OR=2.35) and young

participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48). The SUA cutoff points for risk of obesity using ROC curves were approximately consistent with the international standard.

Conclusions: Our study observed higher SUA level was associated with increased risk of obesity. More high-quality research is needed to further support these findings.

Keywords: serum uric acid, obesity, generalized estimation equation model, risk factors, China

Strengths and limitations of this study

- This is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China.
- The study analysis was based on the GEE model which can increase the accuracy of the prediction.
- The results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.
- The younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

Introduction

An individual's health behavior can influence both physical health and ability to recover from an illness. Annual medical checkup is an example of a positive health behavior, as this preventative measure is associated with earlier disease detection, greater treatment success, and faster recovery from a disease [1]. For this reason, medical data obtained from primary care is a useful source as it includes information on symptoms and health care utilization, all beneficial for use in prediction analysis. Medical checkup data often includes a variety of diagnostic tests to assess health status for early detection and disease prevention. Additionally, medical checkup data provides valuable information on present and past health conditions that are generally difficult to obtain in most population-based data [2].More specifically, medical checkup data is a reliable and objective measure for identifying chronic diseases such as hyperuricemia and obesity.

Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting in hyperuricemia[3, 4]. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and 7.9% for women[5]. Additionally, in 2019 the obesity prevalence was nearing 12% in China. Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was reported to be independently correlated with changes in uric acid concentration, there might be an interaction between them as suggested in prior pathophysiological and metabolic studies [6]. Epidemiological and clinical evidence supports a strong significant positive association between SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq [7]. A cross-sectional study showed that body mass index (BMI) significantly increases with elevated SUA among 27,009 middle-aged and elderly Chinese adults [8]. Previous research showed that hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis[9]. With the increasing prevalence of obesity among adults with hyperuricemia, it is of public health importance to evaluate the long-term epidemiological transitions to develop policies centered on intervention.

Numerous trend analyses have reported the association between SUA and BMI based on short-term survey data in China[10, 11]. However, there remains a gap in evidence regarding the long-term trend for providing estimates on the risks of obesity among Chinese adults during the last two decades. Therefore, the present study aimed to examine the relationship between SUA and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

Methods

Study design and subjects

We conducted a large retrospective study in China. Medical examinations were performed in 2010 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical checkups; (2) absence of blood biochemical examination; and (3) no documented information on BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

Measurements

All participants were invited to join an in-person evaluation that included physical examination and laboratory testing. Physical examinations were conducted following a standardized protocol, including weight, height, waist circumference, hip circumference, and blood pressure. Waist circumference was measured around the midway between the lowest border of the ribs and iliac crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated measurements in the presence of researchers. Laboratory measurements were obtained to measure SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).

Outcomes and definitions

Hyperuricemia was defined as having SUA concentrations>7.0 mg/dL (416.4μmol/L) in men or>6.0 mg/dL (356.9μmol/L) in women[12, 13]. SUA levels were categorized into two groups (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The high SUA level group was classified as participants with hyperuricemia. BMI was defined as weight divided by height^2 (kg/m^2) and categorized into two groups (non-obese [< 28 kg/m^2] and obese [≥28kg/m^2]) based on the Asia-Pacific criteria set by the World Health Organization [14, 15]. We excluded patients taken drugs that might affect uric acid metabolism, such as losartan, furosemide, and allopurinol.

Statistical analysis

We conducted descriptive analysis to present the characteristics of baselines participants. Continuous variables were reported as mean ± standard derivation (SD) and categorical variables as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese and non-obese) were performed using Student' t-tests for continuous variables and Chi-square analyses for categorical variables. Logistic regression model (LRM) was used to evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also utilized generalized estimating equations (GEE) models with unstructured correlation structures to quantify their longitudinal association between SUA and risk of obesity [16], given the data on SUA and obesity were repeatedly measured over the 9-year study period. All models were adjusted for age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 μmol/L or per-SD increase in SUA.

We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age group (youth<65 years vs. elderly ≥65 years). Additionally, we calculated the cut-off values of SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria

including (1) the point on the curve with minimum distance from the left-upper corner of the unit square; and (2) the point where the Youden's index is maximum[17]. A two-sided p-value less than 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

There were no patient and/or public involvement in the design of this study.

Results

There were 15,959 participants (10,023 males) included in this study. The average number of health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD: 13.27) and a mean SUA of 367.05μmol/L (SD: 97.97) at baseline, respectively. There were 1,227 (7.6%) participants that were obese at baseline. Significant differences between the obese and non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR (p-value < 0.001) **(Table 1)**. In total, the prevalence of obesity was approximately 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The prevalence of obesity significantly increased with the number of medical checkup years in the group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078 participants developed obesity over the 9-year period.

As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for SUA [per-1OR=1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.84 (95% CI: 1.77,1.90)], age [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic regression analysis (Model 1). When converted to categorical analysis, the risks of obesity were

greater among those with high level of SUA, males and younger participants. Likewise, with longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2), consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1 OR= 1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.85 (95% CI: 1.77,1.91)] for SUA, OR=1.45 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by categorical variables, we observed similar results with higher risk in male and elderly participants.

As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup analyses. Significant associations between SUA and risk of obesity were observed, where female [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an elevated risk. We also did the analysis of baseline uric acid values vs obesity at the 9-year mark in males and females, respectively where one eliminates baseline cases with hypertension, diabetes or elevated BS, dyslipidemia, normal kidney function, baseline obesity. This result was consistent with the subgroup analysis and well validate the data.

To calculate the discrimination ability of SUA among obese participants at different times of medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the overall cut-off values of SUA were 429.5μmol/L (range: 411.5-488.5 μmol/L) in males and326.9μmol/L (range: 298.5-426.5 μmol/L) in females when stratified by different times of medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5 μmol/L (range: 366.7-431.5 μmol/L) in males and 326.9 μmol/L (range: 301.5-362.1 μmol/L) in females when stratified by different years of medical checkups.

Discussion

To the best of our knowledge, this is the first longitudinal study that estimated the relationship between SUA and obesity over a long time period in China. The prevalence of obesity was approximately 14.2% for high SUA level. Previous studies found that the prevalence of hyperuricemia ranged from 2.5 to 25 % depending on the study population country [18].For instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand[19, 20]. Overall, we found high SUA level was associated with increased risk of obesity, within OR value of 1.85 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies [21, 22]. Currently, obesity and hyperuricemia, as well as their associated health complications (e.g. metabolic syndrome) have emerged as a major public health concern as a result of the growing prevalence, and the estimated economic burden[7].

Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity, suggesting the influence of overproduction and poor renal excretion[23]. Prior studies reported that increased SUA level is closely related to excessive production of UA and the reduction of urinary uric acid excretion and clearance [24]. This ultimately leads to increased risk of patients with visceral fatty obesity[23]. Visceral fat accumulation (VFA) results in a large influx of plasma free fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and subsequently produced large amounts of UA through the activated UA synthesis pathway[25, 26]. Additionally, many researchers have reported a significant correlation between VFA and BMI[27, 28]. Therefore, because of the close biological relationship between UA and BMI, it is of great importance for preventive medicine to pay attention to the interaction between UA and BMI.

Conflicting results regarding gender and age differences for the association between SUA and obesity have been reported[10, 29].Our study found significant differences in obesity participants with elevated OR value among high SUA level, male, and elderly for all medical checkup participants. A similar study reported a positive relationship between BMI and SUA levels among healthy individuals in China[30]. Nevertheless, in this study the subgroup analyses showed that significant

associated risk between SUA and obesity were observed higher in female and young participants. This is consistent with a Thailand study that reported high SUA concentrations were associated with greater risk of obesity in females[31]. However, study in Bangladesh and Japan reported that elevated SUA predicted obesity higher in males and the elderly[8, 29, 31]. Perhaps the associations of SUA with obesity varies by populations. Moreover, in a 10-year follow-up study, BMI was observed to significantly increase with higher SUA levels regardless of race and gender [32]. Therefore, greater attention should be provided to those vulnerable populations in clinical guidelines.

An important observation was that association between SUA and risk of obesity in the LRM [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE model [OR= (1.85 (1.77,1.91)] for 9-year all participants. The risk of obesity within hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can reflect the development of chronic diseases[33]. Regarding the assessment of cut-off values from ROC of SUA in obesity participants, the cut-off values of SUA were 429.5μmol/L in malesand326.9μmol/L in females in stratified analysis by times or years of medical checkup. The cut-off value was approximately consistent with the international standard for males[34]. However, it was underestimated for women in the group of obese participants. Perhaps the proportion of females were fewer in this study. The cut-off values for SUA in the study may be useful for distinguishing tests among obesity and non-obesity participants, which were significant for certain risk value prediction and guidance[35].

To our knowledge, we must note several limitations in the present study. First, the underlying mechanism by which SUA is increased in obese individuals remains not well understood. Second, this study did not collect information on whether participants were prescribed medication to treat hyperuricemia. Additionally, some medications used to treat hypertension may increase uric acid levels. Third, there are numerous confounding factors that have not been considered, which can be

studied together with questionnaires in the future. Moreover, the younger screening population in this study may underestimate the increased risk of uric acid among the elderly obese.

The present study has several strengths that must be noted. First, to our knowledge this is the first large long-term medical checkup study to explore the relationship between SUA and obesity in China. Second, the study analysis was based on the GEE model with high quality data by controlling for confounding factors, which can increase the accuracy of the prediction. Third, participants were representative of the general population with regard to clinical checkup and obesity status, enhancing the generalizability of our findings. Moreover, results from this study could inform prevention methods for obesity, especially in medically underserved areas where medical service is insufficient.

This study filled current gaps in literature by analyzing the relationship between SUA and obesity using medical checkup data. We observed that medical checkup data can be used to improve the risk of obesity prediction accuracy. The medical checkup data used in this study can help provide information that will facilitate intervention development and adoption at the individual level [36]. The utility of medical checkup data can potentially reach beyond predictive power alone in the near future.

Conclusions

In conclusion, our study observed significant associations between SUA and obesity in this 9-year longitudinal study. We mainly found higher SUA level was associated with increased risk of obesity. The prevalence of obesity was approximately 14.2%and significantly increased with the number of medical checkup years in the group with high level of SUA. Additionally, the increased risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses revealed significant associations between SUA and obesity with higher risk for females and young

participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent with the international standard. More evidence from well-designed studies are needed to confirm our findings.

Author Contributions:

Guowei Li, Jie Zeng,Guanming Li: conceived and designed the study.

Guowei Li, Jie Zeng, Wayne R. Lawrence, Jun Yang: acquired data, performed statistical analyses and interpretation, and drafted the manuscript.

Junzhang Tian, Cheng Li, Wanmin Lian, Jingjun He, Hongying Qu, Xiaojie Wang, Hongmei Liu: provided professional and statistical support, and made several critical revisions to the manuscript.

All authors read and approved the final manuscript.

Acknowledgments:

None declared.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

Ethics approval:

The study was approved by Guangdong Second Provincial General Hospital Ethics Committee (reg. no. 20190717-01(2)-YXKXYJ-KT). The need for consent was waived due to the retrospective nature of this study.

Data availability statement:

All data relevant to the study are included in the article or uploaded as supplementary information.

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Tables and Figure legends:

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Table3. Relationship between risk factors and risk of obesity in the models.

Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Figure 1. Location of Guangdong Second Provincial General Hospital (Guangzhou, Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.

Figure 2. Flow diagram showing selection process of participants in our study.

Supplemental data:

Supplementary Figure1. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different times of medical checkups.

Supplementary Figure2. The ROC curves showing the relationship between SUA and risk of obesity stratified by gender and different years of medical checkups (from 2010 to 2018).

Table 1. Baseline characteristics and comparison between obesity and non-obesity participants.

Characteristics	All patients	Obesity[a]	Non-obesity	*p*-value[b]
	n=15959	n=1227	n=14732	
SUA (μmol/L) [SD]	367.05 (97.97)	434.95 (97.65)	361.32 (95.82)	<0.001
Age (years) [SD]	37.38 (13.27)	40.40 (13.40)	37.13 (13.23)	<0.001
Male [n, (%)]	10023 (62.8)	1012 (82.5)	9011 (61.2)	<0.001
SBP (mmHg) [SD]	121.09 (15.85)	131.78 (16.47)	120.19 (15.47)	<0.001
DBP (mmHg) [SD]	73.84 (10.31)	81.16 (11.41)	73.23 (9.97)	<0.001
TC (mmol/L) [SD]	4.88 (0.93)	5.19 (0.95)	4.86 (0.93)	<0.001
TG (mmol/L) [SD]	1.46 (1.10)	2.18 (1.49)	1.40 (1.04)	<0.001
HDL-c (mmol/L) [SD]	1.26 (0.25)	1.15 (0.22)	1.27 (0.25)	<0.001
LDL-c (mmol/L) [SD]	2.92 (0.78)	3.20 (0.80)	2.90 (0.77)	<0.001
FPG (mmol/L) [SD]	5.06 (1.04)	5.51 (1.61)	5.03 (0.97)	<0.001
BUN (mmol/L) [SD]	4.78 (1.25)	5.07 (1.30)	4.75 (1.24)	<0.001
CR (mmol/L) [SD]	94.57 (17.12)	100.05 (16.17)	94.11 (17.12)	<0.001

Note: Continuous variables are presented as the means (standard derivation); SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Cr, creatinine.

[a] Obesity was defined as body mass index (BMI) ≥28.0 kg/m^2.

[b] *p* value for the difference of variables between the two data sets based on independent sample t-test or chi-square test.

*The average number of health checkup for each participant is 2.62.

Table 2. The prevalence of obesity by gender, age of checkup stratified by baseline SUA.

Variable	Obesity prevalence, n (%) [a]		
	Normal SUA	High SUA	P-value
Gender			
Male	357/5280 (6.8)	570/3768 (15.1)	<0.001
Female	104/4431 (2.3)	97/937 (10.3)	<0.001
Age group			
<30	88/3509 (2.5)	168/1643 (10.2)	<0.001
30-44	182/3736 (4.9)	309/1692 (18.3)	<0.001
45-59	121/1727 (7.0)	125/865 (14.5)	<0.001
60-74	54/606 (8.9)	53/378 (14.0)	<0.001
≥75	11/134 (8.2)	12/127 (9.4)	<0.001
Overall	456/9711 (4.6)	669/4705 (14.2)	<0.001

Note: High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

[a]Obesity prevalence = (n of obesity) / (total participants).

Table 3. Relationship between risk factors and risk of obesity in the models.

Variable	Model 1[c]		Model 2[d]	
	OR[a] *(95%CI*[b]*)*	*p*-value	*OR*[a] *(95%CI*[b]*)*	*p*-value
Continuous analysis				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.84 (1.77,1.90)	<0.001	1.85 (1.77,1.91)	<0.001
Gender [n, (%)]				
Female	Reference		Reference	
Male	1.27 (1.16,1.39)	<0.001	1.45 (1.32,1.60)	<0.001
Age (years)	1.02 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001
Categorical analysis				
SUA[e]				
Normal SUA	Reference		Reference	
High SUA	2.02 (1.84, 2.23)	<0.001	2.57 (2.31, 2.87)	<0.001
Gender				
Female	Reference		Reference	
Male	1.25 (1.09, 1.43)	0.002	1.69 (1.59, 1.79)	<0.001
Age group				
<30	Reference		Reference	
30-44	1.38 (1.14, 1.66)	0.001	1.73 (1.54, 1.91)	<0.001
45-59	1.07 (0.89, 1.30)	0.475	1.94 (1.72, 2.18)	<0.001
60-74	1.12 (0.90, 1.38)	0.314	1.99 (1.72, 2.32)	<0.001
≥75	0.95 (0.71, 1.27)	0.718	1.86(1.50, 2.31)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model 1 was adjusted for the variables of SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on the first time of medical checkup participants by using multivariate logistic regression model (LRM).

[d]Model 2 was adjusted for the variables of repeated times or years of medical checkup, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

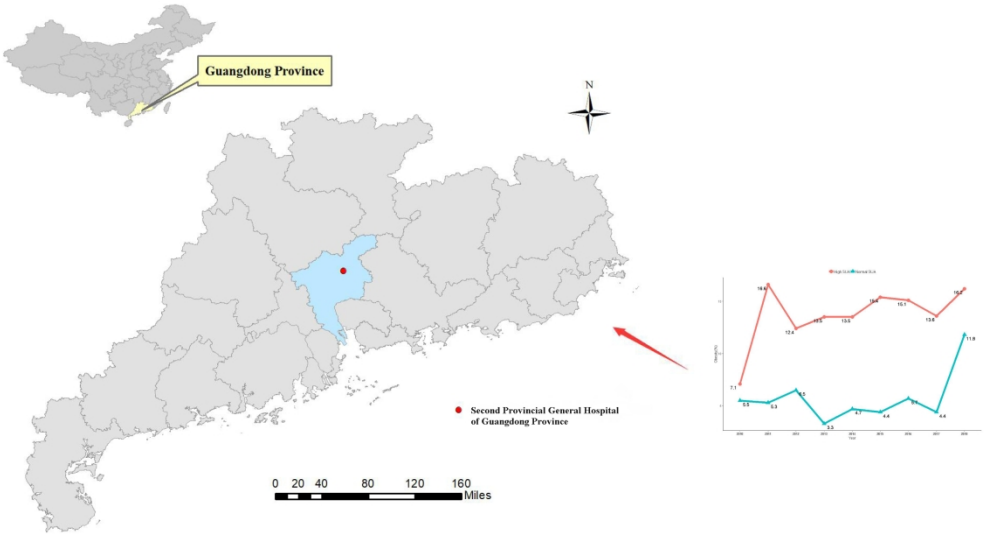
Table 4. Relationship between risk factors and risk of obesity in the models stratified by gender and age group.

Variable	Generalized estimation equation model (GEE)[c]			
Gender	**Male**		**Female**	
	OR[a] (95%CI[b])	***p*-value**	***OR[a] (95%CI[b])***	***p*-value**
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.40 (2.23,2.59)	<0.001	3.79 (3.23,4.45)	<0.001
Age group	**Youth (<65 year)**		**Elderly (≥65 year)**	
	OR[a] (95%CI[b])	***p-value***	***OR[a] (95%CI[b])***	***p-value***
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.00 (1.00,1.01)	<0.001
Per-SD	1.87 (1.80,1.94)	<0.001	1.48 (1.34,1.62)	<0.001
Categorical variables				
SUA				
Normal SUA	Reference		Reference	
High SUA	2.78 (2.58,2.99)	<0.001	1.99 (1.63,2.43)	<0.001

Note: [a]OR: odds ratio; [b]CI: confidence interval.

[c]Model was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

[e]High SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.



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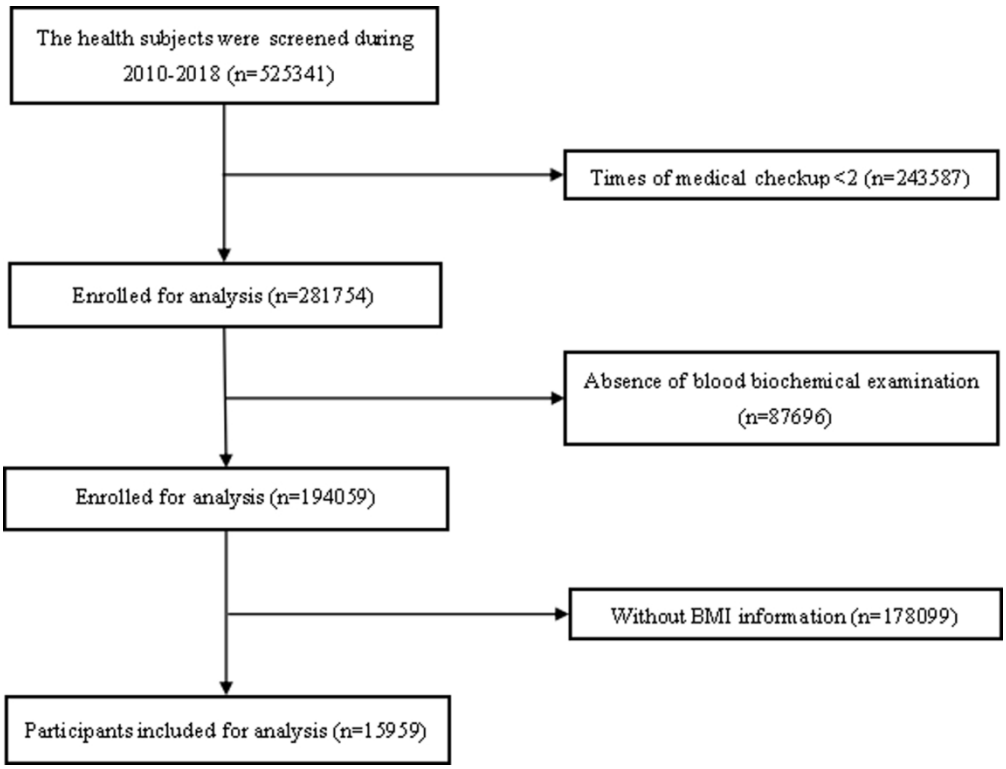

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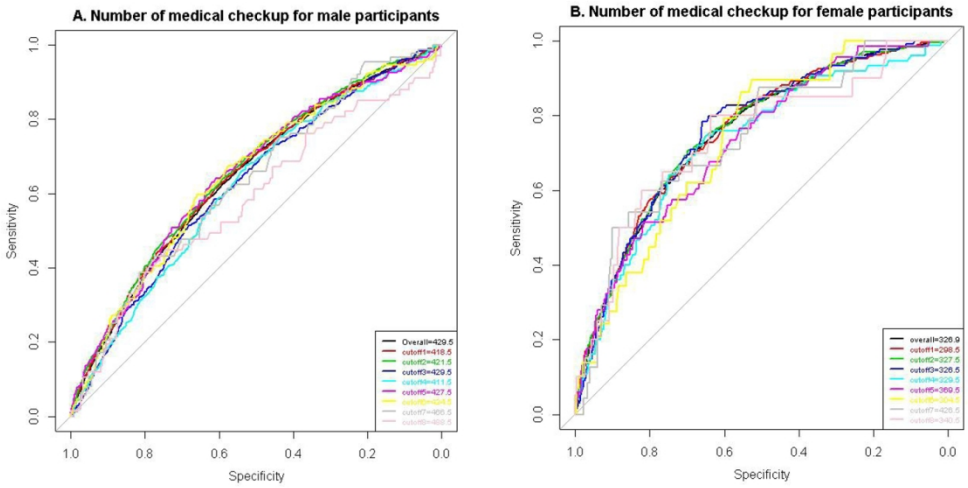

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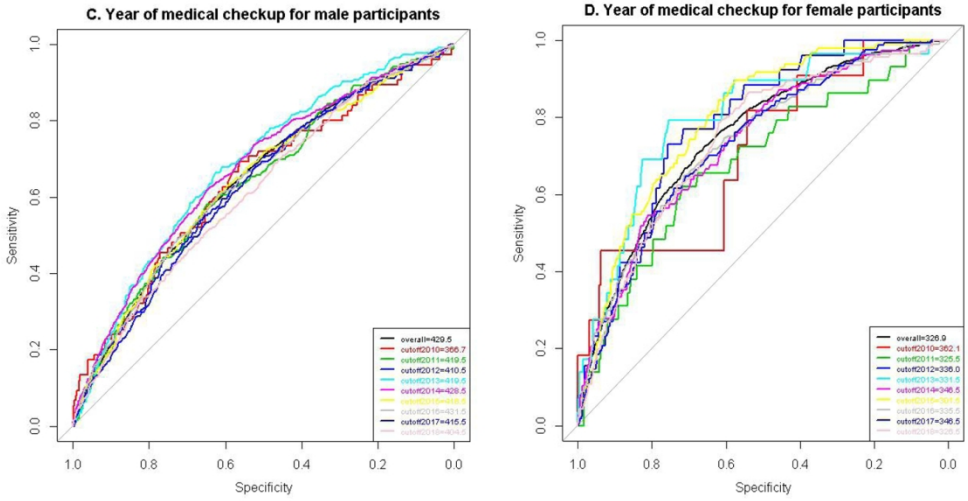

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	7-8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e*) Describe any sensitivity analyses	8-9

Continued on next page

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	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	9-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	9-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	9-10
		Cross-sectional study—Report numbers of outcome events or summary measures	9-10
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
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	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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.