

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041919
Article Type:	Original research
Date Submitted by the Author:	23-Jun-2020
Complete List of Authors:	Zeng, Jie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Lawrence, Wayne R Yang, Jun Tian, Junzhang Li, Guanming Lian, Wanmin He, Jingjun Qu, Hongying Wang, Xiaojie Li, Cheng Li, Guowei
Keywords:	Public health < INFECTIOUS DISEASES, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Jie Zeng¹, Wayne R. Lawrence², Jun Yang³, Junzhang Tian¹, Guanming Li¹, Wanmin Lian⁴,
Jingjun He⁵, Hongying Qu^{1,5}, Xiaojie Wang¹, Cheng Li^{6*}, and Guowei Li^{1,7*}

¹ Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, Guangzhou, China.

² Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, State University of New York, One University Place, Rensselaer, New York.

³ Institute for Environmental and Climate Research, Jinan University, Guangzhou, 511443, China.

⁴ Center for Information, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁵ Center for Health Management and Examination, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁶ Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁷ Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada.

*Corresponding Authors:

Guowei Li, PhD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Department of HEI, McMaster University, Hamilton, Canada L8S 4L8

Telephone: 86-020-89169025; Fax: 86-020-89168021

E-mail: liguowei099@126.com

and

Cheng Li, MD

Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong Second Provincial General Hospital, Guangzhou, 510317, China.

Telephone: 86-020-32640264; Fax: 86-020-32640184

E-mail: lywergd@163.com

Word count: 2,822

1 Abstract

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

6
7 **Methods:** Data were collected at Guangdong Second Provincial General Hospital in Guangzhou
8 City, China between January 2010 and December 2018. Participants with medical checkup ≥ 2
9 times were included in our analyses. Physical examinations and laboratory measurement variables
10 were obtained from the medical checkup system. The high SUA level group was classified as
11 participants with hyperuricemia, and obesity was defined as $BMI \geq 28 \text{ kg/m}^2$. Logistic regression
12 model (LRM) was performed for data at baseline. For all participants, generalized estimation
13 equation (GEE) model was used to assess the association between SUA and obesity, where the
14 data were repeatedly measured over the nine-year study period. Subgroup analysis was performed
15 by gender and age group. We calculated the cut-off values for SUA of obesity using the receiver
16 operating characteristic curves (ROC) technique.

17
18 **Results:** A total of 15,959 participants (10,023 males and 5,936 females) were included in this
19 study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 $\mu\text{mol/L}$ (SD:
20 97.97) at baseline, respectively. The prevalence of obesity was approximately 14.2% for high
21 SUA level. In logistic regression analysis at baseline, we observed a positive association between
22 SUA and risk of obesity: $OR=1.84$ (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering
23 repeatedly measured over 9-year for all participants in GEE model, the per-SD OR was 1.85 (95%
24 CI:1.77,1.91) for SUA and the increased risk of obesity was greater for male ($OR=1.45$) and
25 elderly participants ($OR=1.01$). In subgroup analyses by gender and age, we observed significant
26 associations between SUA and obesity with higher risk in female ($OR=2.35$) and young
27 participants ($OR=1.87$) when compared to male ($OR=1.70$) and the elderly participants

1
2
3
4 28 (OR=1.48). The SUA cut off points for risk of obesity using ROC curves were approximately
5
6 29 consistent with the international standard.
7
8
9 30

10
11 31 **Conclusions:** Our study found higher SUA level was associated with increased risk of obesity.
12
13 32 More high-quality research is needed to further support this finding.
14
15 33

16
17
18 34 **Keywords:** serum uric acid, obesity, generalized estimation equation model, risk factors, China
19
20 35
21
22
23 36
24
25
26 37
27
28
29 38
30
31 39
32
33 40
34
35
36 41
37
38
39 42
40
41 43
42
43
44 44
45
46
47 45
48
49
50 46
51
52
53 47
54
55 48
56
57
58 49
59
60

1
2
3
4 50 **Strengths and limitations of this study**
5

6 51 ➤ This is the first large long-term medical checkup study to explore the relationship between
7
8 52 SUA and obesity in China.
9

10 53 ➤ The study analysis was based on the GEE model which can increase the accuracy of the
11
12 54 prediction.
13

14
15 55 ➤ The results from this study could inform prevention methods for obesity, especially in
16
17 56 medically underserved areas where medical service is insufficient.
18

19
20 57 ➤ The younger screening population in this study may underestimate the increased risk of uric
21
22 58 acid among the elderly obese.
23

24
25 59
26

27
28 60
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

61 Introduction

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

72
73 Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting
74 in hyperuricemia ^{3,4}. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and
75 7.9% for women ⁵. Additionally, in 2019 the obesity prevalence was nearing 12% in China.
76 Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was
77 reported to be independently correlated with changes in uric acid concentration, there might be an
78 interaction between them as suggested in prior pathophysiological and metabolic studies ⁶.
79 Epidemiological and clinical evidence supports a strong significant positive association between
80 SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq ⁷. A cross-
81 sectional study showed that body mass index (BMI) significantly increases with elevated SUA
82 among 27,009 middle-aged and elderly Chinese adults ⁸. Previous research showed that
83 hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis ⁹. With the
84 increasing prevalence of obesity among adults with hyperuricemia, it is of public health
85 importance to evaluate the long-term epidemiological transitions to develop policies centered on
86 intervention.

87

1
2
3
4 88 Numerous trend analyses have reported the association between SUA and BMI based on short-
5
6 89 term survey data in China^{10, 11}. However, there remains a gap in evidence regarding the long-term
7
8 90 trend for providing estimates on the risks of obesity among Chinese adults during the last two
9
10 91 decades. Therefore, the present study aimed to examine the relationship between SUA and risk of
11
12 92 obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

13
14 93

16 94 **Methods**

17 95 **Study design and subjects**

18
19
20
21
22 96 We conducted a large retrospective study in China. Medical examinations were performed in 2010
23
24 97 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China
25
26 98 (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical
27
28 99 checkup; (2) absence of blood biochemical examination; and (3) no documented information on
29
30 100 BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

31
32 101

33 102 **Measurements**

34
35
36
37 103 All participants were invited to participate in an in-person evaluation which included physical
38
39 104 examination and laboratory testing. Physical examinations were conducted following a
40
41 105 standardized protocol, including weight, height, waist circumference, hip circumference, and
42
43 106 blood pressure. Waist circumference was measured around the midway between the lowest border
44
45 107 of the ribs and iliac crest in the horizontal plane. The quality of anthropometric data was
46
47 108 confirmed by repeated measurements in the presence of researchers. Laboratory measurements
48
49 109 were obtained to measure SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP),
50
51 110 total cholesterol (TC), triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein
52
53 111 cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea
54
55 112 nitrogen (BUN).

56
57
58 113
59
60

114 **Outcomes and definitions**

115 Hyperuricemia was defined as having SUA concentrations >7.0 mg/dL ($416.4\mu\text{mol/L}$) in men
116 or >6.0 mg/dL ($356.9\mu\text{mol/L}$) in women^{12,13}. SUA levels were categorized into two groups
117 (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The
118 high SUA level group was classified as participants with hyperuricemia. BMI was defined as
119 weight divided by height² (kg/m^2). Meanwhile, it was categorized into two groups (non-obese [$<$
120 28 kg/m^2] and obese [≥ 28 kg/m^2]) based on the Asia-Pacific criteria set by the World Health
121 Organization^{14,15}. We excluded patients taken drugs that might affect uric acid metabolism, such
122 as losartan, furosemide, and allopurinol. This study was approved by the Guangdong Second
123 Provincial General Hospital.

125 **Statistical analysis**

126 We conducted descriptive analysis examining baselines participants. Continuous variables were
127 reported as mean \pm standard derivation and categorical variables as frequency and percentage,
128 unless otherwise specified. Comparisons between two groups (obese and non-obese) were
129 performed using Student t-tests for continuous variables and Chi-square analyses for categorical
130 data. Logistic regression model (LRM) was used to evaluate the relationship between risk of
131 obesity and risk factors for the data at baseline. We also utilized generalized estimating equations
132 (GEE) models with unstructured correlation structures to quantify their association between SUA
133 and risk of obesity¹⁶, given the data on SUA and obesity were repeatedly measured over the 9-
134 year study period. All the models were adjusted for age, gender, SBP, DBP, TC, TG, HDL-c,
135 LDL-c, FPG, BUN, and CR in each group. Results were presented as odds ratio (OR) and 95%
136 confidence interval (CI) with per-1 $\mu\text{mol/L}$ or per-SD increase in SUA.

137
138 We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age
139 group (young <65 years vs. elderly ≥ 65 years). Additionally, we calculated the cut-off values of
140 SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on the

1
2
3
4 141 criteria including that (1) the point on the curve with minimum distance from the left-upper corner
5
6 142 of the unit square; and (2) the point where the Youden's index is maximum ¹⁷. A two-sided p-
7
8 143 value less than 0.05 was considered as the statistically significant. Analyses were performed using
9
10 144 R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

11
12 145

146 **Patient and public involvement**

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

148

149 **Results**

150 There were 15,959 participants (10,023 males) included in this study. The average number of
151 health checkup for each participant was 2.62. The participants had a mean age of 37.38 (SD:
152 13.27) and a mean SUA of 367.05 (SD: 97.97) at baseline, respectively. There were 1,227 (7.6%)
153 participants that were obese at baseline. Significant differences between the obese and non-obese
154 groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR
155 (p-value < 0.001) (**Table 1**). In total, the prevalence of obesity was approximately 14.2% for high
156 SUA level. Obesity prevalence significantly increased with elevating SUA in the subgroup
157 analysis by gender and age group (p-value < 0.001). The prevalence was higher in males when
158 compared to females. However, the prevalence had no obvious trend for different age groups
159 (**Table 2**). The prevalence of obesity significantly increased with the number of medical checkup
160 years in the group with high SUA and normal SUA level (p<0.001 for trend) (**Figure 1**).

161

162 As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for
163 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
164 [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic
165 regression analysis (Model 1). When converted to categorical analysis, the OR value for SUA was
166 greater for high level SUA compared to normal SUA. Additionally, the OR value was higher for

1
2
3
4 167 elderly than young participants. Likewise, in the multivariable GEE model (Model 2) based on all
5
6 168 medical checkup participants, consistent risk factors for obesity were obtained. The estimates were
7
8 169 observed as follows: [per-1 OR= 1.01 (95% CI: 1.01,1.02)] or [per-SD OR=1.85 (95% CI:
9
10 170 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.
11
12 171 In additional analysis by categorical variables, we observed similar results with higher risk in male
13
14 172 and elderly participants.
15

16 173

17
18
19 174 As shown in **Table 4**, similar results for GEE model analyses were observed in subgroup analyses.
20
21 175 Significant associations between SUA and obesity were observed, where female [per-SD OR=2.35
22
23 176 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an elevated risk. To
24
25 177 calculate the discrimination ability of SUA among obese participants at different times of medical
26
27 178 checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were
28
29 179 calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver
30
31 180 operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the
32
33 181 overall cut-off values of SUA in males were 429.5 μ mol/L (range: 411.5-488.5 μ mol/L) and in
34
35 182 females were 326.9 μ mol/L (range: 298.5-426.5 μ mol/L) when stratified by different times of
36
37 183 medical checkups. Similarly, we calculated the overall cut-off values for SUA , which was 429.5
38
39 184 μ mol/L (range: 366.7-431.5 μ mol/L) in males and was 326.9 μ mol/L (range: 301.5-362.1 μ mol/L)
40
41 185 in females when stratified by different years of medical checkups.
42

43 186

44 187 **Discussion**

45
46
47
48 188 To the best of our knowledge, this is the first longitudinal study that estimated the relationship
49
50 189 between SUA and obesity over a long time period in China. The prevalence of obesity was
51
52 190 approximately 14.2% for high SUA level. Previous studies found the prevalence of hyperuricemia
53
54 191 ranges from 2.5 to 25 % depending on the study population country¹⁸. For instance, the
55
56 192 prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand^{19,20}. Overall, we
57
58 193 found high SUA level was associated with increased risk of obesity, within OR value of 1.85
59

1
2
3
4 194 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies ²¹,
5 195 ²². Currently, obesity and hyperuricemia, as well as their associated health complications (e.g.
6
7 196 metabolic syndrome) have emerged as a major public health concern as a result of the growing
8
9 197 prevalence, and the estimated economic burden ⁷.

10
11
12 198

13
14
15 199 Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity,
16
17 200 suggesting the influence of overproduction and poor renal excretion ²³. Prior studies reported that
18
19 201 increase SUA level is closely related to excessive production of UA and the reduction of urinary
20
21 202 uric acid excretion and clearance ²⁴. Ultimately leading to increased risk of patients with visceral
22
23 203 fatty obesity ²³. Visceral fat accumulation (VFA) results in a large influx of plasma free fatty acids
24
25 204 into the portal vein and liver. This stimulates the synthesis of triglycerides and subsequently
26
27 205 produced large amounts of UA through the activated UA synthesis pathway ^{25,26}. Additionally,
28
29 206 many researchers have reported a significant correlation between VFA and BMI ^{27,28}. Therefore,
30
31 207 because of the close biological relationship between UA and BMI, it is of great importance for
32
33 208 preventive medicine to pay attention to the interaction between UA and BMI.

34
35 209

36
37 210 Conflicting results regarding gender and age differences for the association between SUA and
38
39 211 obesity have been reported ^{10,29}. Our study found significant differences in obesity participants
40
41 212 with elevated OR value among high SUA level, male, and elderly for all medical checkup
42
43 213 participants. A similar study reported a positive relationship between BMI and SUA levels among
44
45 214 healthy individuals in China ³⁰. Nevertheless, in this study the subgroup analyses showed that
46
47 215 significant associated risk between SUA and obesity were observed higher in female and young
48
49 216 participants. This is consistent with a Thailand study that reported high SUA concentrations were
50
51 217 associated with greater risk of obesity in females ³¹. However, a Bangladeshi study and a Japanese
52
53 218 study reported that elevated SUA predicted obesity higher in males and the elderly ^{8,29,31}. Perhaps
54
55 219 the associations of SUA with obesity varies based on population. Moreover, in a 10-year follow-
56
57 220 up study, BMI was observed to significantly increase with higher SUA levels regardless of race

1
2
3
4 221 and gender³². Therefore, greater attention should be provided to these vulnerable populations in
5
6 222 clinical guidelines.

7
8 223

9
10
11 224 An important observation was that the association between SUA and risk of obesity in the LRM
12
13 225 [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in GEE model
14
15 226 [OR= (1.85 (1.77,1.91))] for 9-year all participants. The risk of obesity within hyperuricemia
16
17 227 remained stable over the years. Therefore, short-term medical checkup results can be reflected the
18
19 228 development of chronic diseases³³. Regarding the assessment of cut-off values from receiver
20
21 229 operating curves (ROC) of SUA in obesity participants, the cut-off values of SUA in males was
22
23 230 429.5 μ mol/L and in females was 326.9 μ mol/L in stratified analysis by times or years of medical
24
25 231 checkup. The cut-off value was approximately consistent with the international standard for males
26
27 232³⁴. However, it was underestimated for women in the group of obese participants. Perhaps the
28
29 233 proportion of females were fewer in this study. The cut-off values of SUA in the study may be
30
31 234 useful for on distinguishing tests among obesity and non-obesity participants, which were
32
33 235 significant for certain risk value prediction and guidance³⁵.

34
35 236

36
37 237 We must note several limitations in the present study. First, the underlying mechanism by which
38
39 238 SUA is increased in obese individuals remains not well understood. Second, this study did not
40
41 239 collect information on whether participants were prescribed medication to treat hyperuricemia.
42
43 240 Third, there are numerous confounding factors that have not been considered, which can be
44
45 241 studied together with questionnaires in the future. Moreover, the younger screening population in
46
47 242 this study may underestimate the increased risk of uric acid among the elderly obese.

48
49
50 243

51
52 244 The present study has several strengths that must be noted. First, to our knowledge this is the first
53
54 245 large long-term medical checkup study to explore the relationship between SUA and obesity in
55
56 246 China. Second, the study analysis was based on the GEE model with high quality data by
57
58 247 controlling for confounding factors, which can increase the accuracy of the prediction. Third,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

252

253 The present study filled current gaps in literature by analyzing the relationship between SUA and
254 obesity using medical checkup data. We observed that medical checkup data can be used to improve
255 risk of obesity prediction accuracy. The medical checkup data used in this study can help provide
256 information that will facilitate intervention development and adoption at the individual level³⁶. We
257 believe that the utility of medical checkup data will reach beyond predictive power alone in the near
258 future.

259

260 **Conclusions**

261 In conclusion, our study observed significant associations between SUA and obesity in this 9-year
262 follow-up data. We mainly found higher SUA level was associated with increased risk of obesity.
263 The prevalence of obesity was approximately 14.2% and significantly increased with the number
264 of medical checkup years in the group of high SUA. Additionally, the increased risk of obesity was
265 greater for high SUA level, male, and elderly participants. Subgroup analyses revealed significant
266 associations between SUA and obesity with higher risk in female and young participants.
267 Additionally, the cut-off for SUA on risk of obesity were approximately consistent with the
268 international standard. More evidence from well-designed studies are needed to confirm our
269 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.

Acknowledgments:

None declared.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

Funding:

Research grants from the Science Foundation of Guangdong Second Provincial General Hospital (YQ2019-008).

Reference

1. Nagahama S, Kashino I, Hu H, Nanri A, Kurotani K, Kuwahara K *et al.* Haemoglobin A1c and hearing impairment: longitudinal analysis using a large occupational health check-up data of Japan. *BMJ open* 2018; **8**(9): e023220.
2. Kim YJ, Park H. Improving Prediction of High-Cost Health Care Users with Medical Check-Up Data. *Big data* 2019; **7**(3): 163-175.
3. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**(9995): 743-800.
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9945): 766-81.
5. Liu R, Han C, Wu D, Xia X, Gu J, Guan H *et al.* Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *BioMed research international* 2015; **2015**: 762820.
6. Ishizaka N, Ishizaka Y, Toda A, Tani M, Koike K, Yamakado M *et al.* Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. *The Journal of rheumatology* 2010; **37**(2): 410-6.
7. Chen MY, Zhao CC, Li TT, Zhu Y, Yu TP, Bao YQ *et al.* Serum uric acid levels are associated with obesity but not cardio-cerebrovascular events in Chinese inpatients with type 2 diabetes. *Scientific reports* 2017; **7**: 40009.
8. Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X *et al.* Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *European journal of epidemiology* 2013; **28**(8): 669-76.
9. Johnson RJ, Lanaspas MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. *Seminars in nephrology* 2011; **31**(5): 394-9.
10. Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. 2018; **13**(11): e0206850.
11. Yang C, Yang S, Feng C, Zhang C, Xu W, Zhang L *et al.* Associations of hyperuricemia and obesity with remission of nonalcoholic fatty liver disease among Chinese men: A retrospective cohort study. *PloS one* 2018; **13**(2): e0192396.
12. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic

- 1
2
3 syndrome in women and men. *Metabolism: clinical and experimental* 2008; **57**(6): 845-52.
4
5
6 13. You L, Liu A, Wuyun G, Wu H, Wang P. Prevalence of hyperuricemia and the relationship
7 between serum uric acid and metabolic syndrome in the Asian Mongolian area. *Journal of*
8 *atherosclerosis and thrombosis* 2014; **21**(4): 355-65.
9
10 14. WHO. Appropriate body-mass index for Asian populations and its implications for policy and
11 intervention strategies. *Lancet* 2004; **363**(9403): 157-63.
12
13 15. Li MF, Ren Y, Zhao CC, Zhang R, Li LX, Liu F *et al*. Prevalence and clinical characteristics of
14 lower limb atherosclerotic lesions in newly diagnosed patients with ketosis-onset diabetes: a
15 cross-sectional study. *Diabetology & metabolic syndrome* 2014; **6**: 71.
16
17 16. Buzkova P, Brown ER, John-Stewart GC. Longitudinal data analysis for generalized linear
18 models under participant-driven informative follow-up: an application in maternal health
19 epidemiology. *American journal of epidemiology* 2010; **171**(2): 189-97.
20
21 17. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off
22 value: the case of tests with continuous results. *Biochemia medica* 2016; **26**(3): 297-307.
23
24 18. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese.
25 *Obesity surgery* 2012; **22**(6): 945-8.
26
27 19. Uaratanawong S, Suraamornkul S, Angkeaw S, Uaratanawong R. Prevalence of hyperuricemia
28 in Bangkok population. *Clinical rheumatology* 2011; **30**(7): 887-93.
29
30 20. Ford DK, Demos AM. Serum Uric Acid Levels of Healthy Caucasian, Chinese and Haida Indian
31 Males in British Columbia. *Canadian Medical Association journal* 1964; **90**: 1295-7.
32
33 21. Kuwabara M, Kuwabara R, Hisatome I, Niwa K, Roncal-Jimenez CA, Bjornstad P *et al*.
34 "Metabolically Healthy" Obesity and Hyperuricemia Increase Risk for Hypertension and
35 Diabetes: 5-year Japanese Cohort Study. *Obesity* 2017; **25**(11): 1997-2008.
36
37 22. Zhang N, Chang Y, Guo X, Chen Y, Ye N, Sun Y. A Body Shape Index and Body Roundness
38 Index: Two new body indices for detecting association between obesity and hyperuricemia in
39 rural area of China. *European journal of internal medicine* 2016; **29**: 32-6.
40
41 23. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T *et al*. Effect of
42 visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity
43 is linked more closely to overproduction of uric acid than subcutaneous fat obesity.
44 *Metabolism: clinical and experimental* 1998; **47**(8): 929-33.
45
46 24. Han T, Meng X, Shan R, Zi T, Li Y, Ma H *et al*. Temporal relationship between hyperuricemia
47 and obesity, and its association with future risk of type 2 diabetes. *International journal of*
48 *obesity (2005)* 2018; **42**(7): 1336-1344.
49
50 25. Fabregat I, Revilla E, Machado A. Short-term control of the pentose phosphate cycle by
51 insulin could be modulated by the NADPH/NADP ratio in rat adipocytes and hepatocytes.
52 *Biochemical and biophysical research communications* 1987; **146**(2): 920-5.
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
26. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism: clinical and experimental* 1981; **30**(6): 616-34.
 27. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circulation journal : official journal of the Japanese Circulation Society* 2002; **66**(11): 987-92.
 28. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S *et al.* Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes research and clinical practice* 2009; **83**(1): 100-5.
 29. Tanaka K, Ogata S, Tanaka H, Omura K, Honda C, Hayakawa K. The relationship between body mass index and uric acid: a study on Japanese adult twins. *Environmental health and preventive medicine* 2015; **20**(5): 347-53.
 30. Wang H, Wang L, Xie R, Dai W, Gao C, Shen P *et al.* Association of Serum Uric Acid with Body Mass Index: A Cross-Sectional Study from Jiangsu Province, China. *Iranian journal of public health* 2014; **43**(11): 1503-9.
 31. Jaipakdee J, Jiamjarasrangsri W, Lohsoonthorn V, Lertmaharit S. Prevalence of metabolic syndrome and its association with serum uric acid levels in Bangkok Thailand. *The Southeast Asian journal of tropical medicine and public health* 2013; **44**(3): 512-22.
 32. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *European journal of epidemiology* 2007; **22**(7): 439-45.
 33. Nohara Y, Kai E. Health checkup and telemedical intervention program for preventive medicine in developing countries: verification study. 2015; **17**(1): e2.
 34. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Current opinion in rheumatology* 2014; **26**(2): 186-91.
 35. Mongioi LM, Condorelli RA, Barbagallo F, Cannarella R, La Vignera S, Calogero AE. Accuracy of the Low-Dose ACTH Stimulation Test for Adrenal Insufficiency Diagnosis: A Re-Assessment of the Cut-Off Value. *Journal of clinical medicine* 2019; **8**(6).
 36. Taninaga J, Nishiyama Y. Prediction of future gastric cancer risk using a machine learning algorithm and comprehensive medical check-up data: A case-control study. 2019; **9**(1): 12384.

1
2
3
4 **Tables and Figure legends:**

5 **Table 1.** Baseline characteristics and comparison between obesity and non-obesity participants.
6
7

8
9 **Table 2.** The prevalence of obesity by gender, age of checkup stratified by baseline SUA.
10
11

12
13 **Table 3.** Relationship between risk factors and risk of obesity in the models.
14
15

16 **Table 4.** Relationship between risk factors and risk of obesity in the models stratified by gender
17 and age group.
18
19

20
21
22 **Figure 1.** Location of Guangdong Second Provincial General Hospital (Guangzhou,
23 Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.
24
25

26
27 **Figure 2.** Flow diagram showing selection process of participants in our study.
28
29

30
31
32
33
34 **Supplemental data:**

35
36
37 **Supplementary Figure 1.** The ROC curves showing the relationship between SUA and risk of
38 obesity stratified by gender and different times of medical checkups.
39
40

41
42 **Supplementary Figure 2.** The ROC curves showing the relationship between SUA and risk of
43 obesity stratified by gender and different years of medical checkups (from 2010 to 2018).
44
45
46
47
48
49
50
51
52
53
54
55
56

57
58 **Table 1.** Baseline characteristics and comparison between obesity and non-obesity participants.
59
60

Characteristics	All patients	Obesity ^a	Non-obesity	<i>p</i> -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/m².

^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.

^aObesity 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: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

^dModel 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).

^eHigh 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.

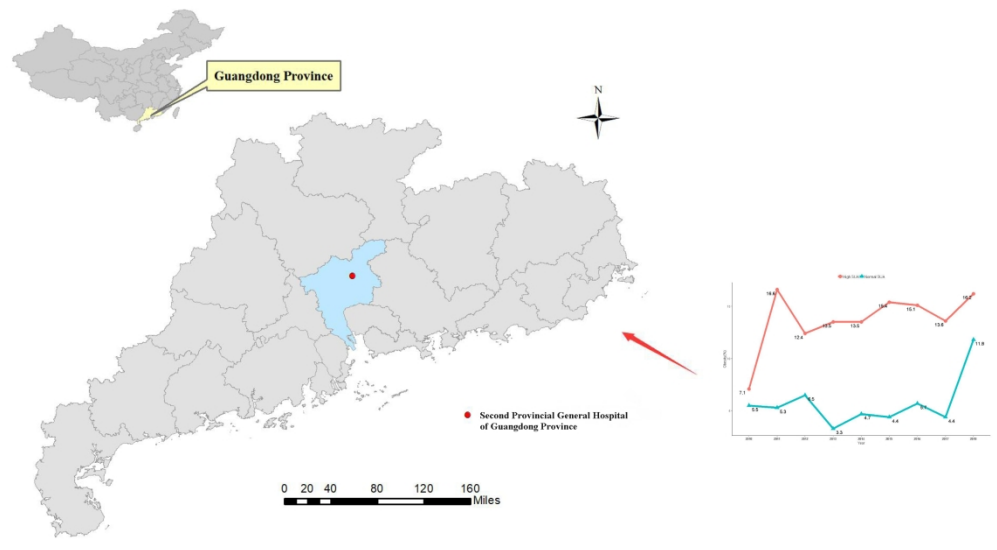
Variable	Generalized estimation equation model (GEE) ^c			
	Male		Female	
Gender	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
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)	
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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: ^aOR: odds ratio; ^bCI: confidence interval.

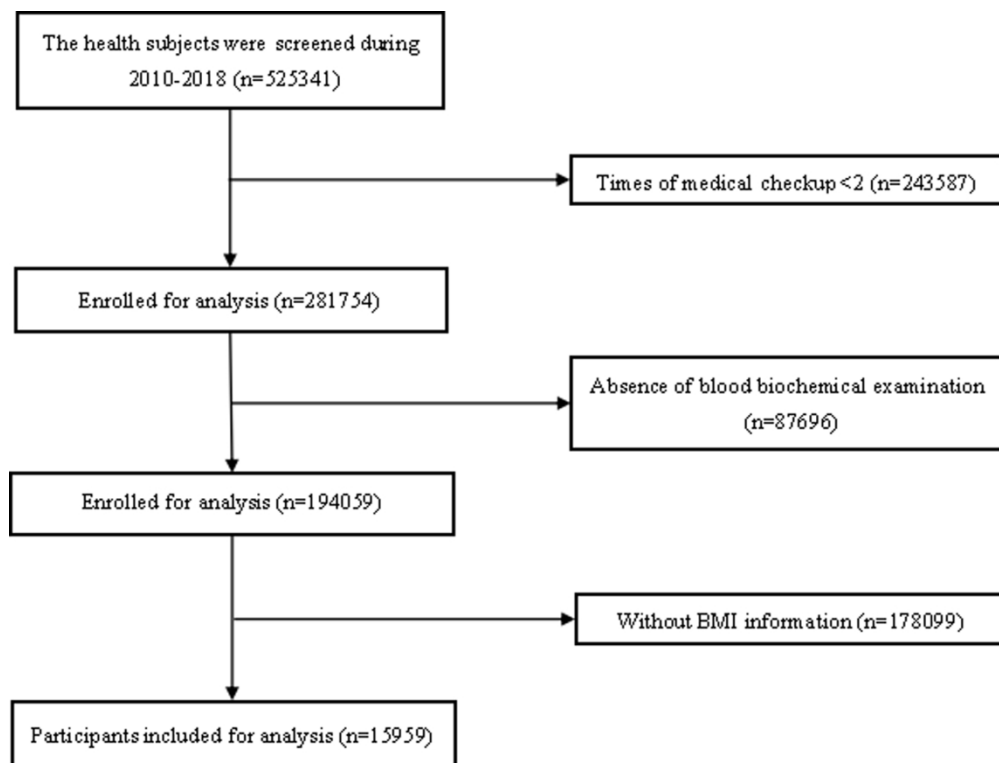
^cModel was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

^eHigh 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

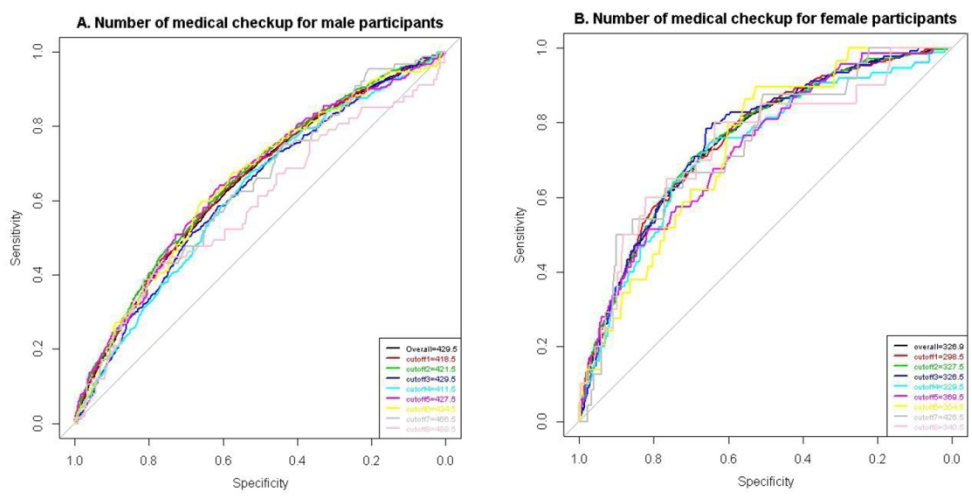


240x140mm (300 x 300 DPI)

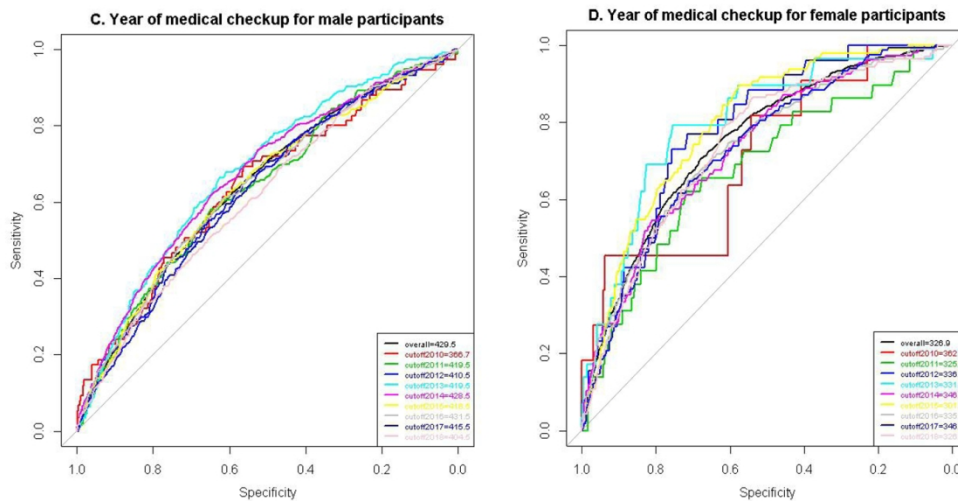


155x117mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



127x63mm (300 x 300 DPI)



127x64mm (300 x 300 DPI)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041919.R1
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2020
Complete List of Authors:	Zeng, Jie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Lawrence, Wayne R; University at Albany State University of New York, Department of Epidemiology and Biostatistics Yang, Jun; Jinan University, Institute for Environmental and Climate Research Tian, Junzhang; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Cheng; Guangdong Second Provincial General Hospital, Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute Lian, Wanmin; Guangdong Second Provincial General Hospital, Center for Information He, Jingjun; Guangdong Second Provincial General Hospital, Center for Health Management and Examination Qu, Hongying; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Wang, Xiaojie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Liu, Hongmei; Guangdong Second Provincial General Hospital, Department of Ultrasound Li, Guanming; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Guowei; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Rheumatology, Public health
Keywords:	Public health < INFECTIOUS DISEASES, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Jie Zeng^{1,2}, Wayne R. Lawrence³, Jun Yang⁴, Junzhang Tian¹, Cheng Li⁵, Wanmin Lian⁶, Jingjun He⁷, Hongying Qu^{1,7}, Xiaojie Wang¹, Hongmei Liu^{2,8}, Guanming Li^{1*}, and Guowei Li^{1,9*}

¹ Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, Guangzhou, China.

² Institute of Ultrasound in Musculoskeletal Sports Medicine, Guangdong Second Provincial General Hospital, Guangzhou, China.

³ Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, State University of New York, One University Place, Rensselaer, New York.

⁴ Institute for Environmental and Climate Research, Jinan University, Guangzhou, 511443, China.

⁵ Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁶ Center for Information, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁷ Center for Health Management and Examination, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁸ Department of Ultrasound, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁹ Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada.

*Corresponding Authors:

Guowei Li, PhD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Department of HEI, McMaster University, Hamilton, Canada L8S 4L8

Telephone: 86-020-89169025; Fax: 86-020-89168021

E-mail: liguowei099@126.com

and

Guanming Li, MD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Telephone: 86-020-32640264; Fax: 86-020-32640184

E-mail: lywergd@163.com

Word count: 2,953

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Abstract

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

6
7 **Methods:** Data were collected at Guangdong Second Provincial General Hospital in Guangzhou
8 City, China between January 2010 and December 2018. Participants with ≥ 2 medical checkup
9 times were included in our analyses. Physical examinations and laboratory measurement variables
10 were obtained from the medical checkup system. The high SUA level group was classified as
11 participants with hyperuricemia, and obesity was defined as $BMI \geq 28 \text{ kg/m}^2$. Logistic regression
12 model (LRM) was performed for data at baseline. For all participants, generalized estimation
13 equation (GEE) model was used to assess the association between SUA and obesity, where the
14 data were repeatedly measured over the nine-year study period. Subgroup analyses were
15 performed by gender and age group. We calculated the cut-off values for SUA of obesity using the
16 receiver operating characteristic curves (ROC) technique.

17
18 **Results:** A total of 15,959 participants (10,023 males and 5,936 females) were included in this
19 study, with an average age of 37.38 years (SD: 13.27) and average SUA of $367.05 \mu\text{mol/L}$ (SD:
20 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year
21 period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic
22 regression analysis at baseline, we observed a positive association between SUA and risk of
23 obesity: $OR=1.84$ (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated
24 measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95%
25 CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male ($OR=1.45$) and
26 elderly participants ($OR=1.01$). In subgroup analyses by gender and age, we observed significant
27 associations between SUA and obesity with higher risk in female ($OR=2.35$) and young

1
2
3
4 28 participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48).

5
6 29 The SUA cut off points for risk of obesity using ROC curves were approximately consistent with
7
8 30 the international standard.
9

10 31

11
12
13 32 **Conclusions:** Our study observed higher SUA level was associated with increased risk of obesity.

14
15 33 More high-quality research is needed to further support these findings.
16

17 34

18
19
20 35 **Keywords:** serum uric acid, obesity, generalized estimation equation model, risk factors, China
21

22 36

23
24
25 37

26
27
28 38

29
30
31 39

32
33 40

34
35
36 41

37
38
39 42

40
41 43

42
43
44 44

45
46
47 45

48
49 46

50
51 47

52
53 48

54
55
56
57 49
58
59
60

1
2
3
4 50 **Strengths and limitations of this study**
5

6 51 ➤ This is the first large long-term medical checkup study to explore the relationship between
7
8 52 SUA and obesity in China.
9

10 53 ➤ The study analysis was based on the GEE model which can increase the accuracy of the
11
12 54 prediction.
13

14
15 55 ➤ The results from this study could inform prevention methods for obesity, especially in
16
17 56 medically underserved areas where medical service is insufficient.
18

19
20 57 ➤ The younger screening population in this study may underestimate the increased risk of uric
21
22 58 acid among the elderly obese.
23

24
25 59
26

27
28 60
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

61 Introduction

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

72
73 Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting
74 in hyperuricemia ^{3,4}. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and
75 7.9% for women ⁵. Additionally, in 2019 the obesity prevalence was nearing 12% in China.
76 Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was
77 reported to be independently correlated with changes in uric acid concentration, there might be an
78 interaction between them as suggested in prior pathophysiological and metabolic studies ⁶.
79 Epidemiological and clinical evidence supports a strong significant positive association between
80 SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq ⁷. A cross-
81 sectional study showed that body mass index (BMI) significantly increases with elevated SUA
82 among 27,009 middle-aged and elderly Chinese adults ⁸. Previous research showed that
83 hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis ⁹. With the
84 increasing prevalence of obesity among adults with hyperuricemia, it is of public health
85 importance to evaluate the long-term epidemiological transitions to develop policies centered on
86 intervention.

87

1
2
3
4 88 Numerous trend analyses have reported the association between SUA and BMI based on short-
5
6 89 term survey data in China ^{10, 11}. However, there remains a gap in evidence regarding the long-term
7
8 90 trend for providing estimates on the risks of obesity among Chinese adults during the last two
9
10 91 decades. Therefore, the present study aimed to examine the relationship between SUA and risk of
11
12 92 obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.
13
14 93

16 94 **Methods**

17 95 **Study design and subjects**

18
19
20
21
22 96 We conducted a large retrospective study in China. Medical examinations were performed in 2010
23
24 97 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China
25
26 98 (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical
27
28 99 checkups; (2) absence of blood biochemical examination; and (3) no documented information on
29
30 100 BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).
31
32 101
33
34

35 102 **Measurements**

36
37 103 All participants were invited to join an in-person evaluation that included physical examination
38
39 104 and laboratory testing. Physical examinations were conducted following a standardized protocol,
40
41 105 including weight, height, waist circumference, hip circumference, and blood pressure. Waist
42
43 106 circumference was measured around the midway between the lowest border of the ribs and iliac
44
45 107 crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated
46
47 108 measurements in the presence of researchers. Laboratory measurements were obtained to measure
48
49 109 SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC),
50
51 110 triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C),
52
53 111 low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).
54
55
56 112

57 113 **Outcomes and definitions**

1
2
3
4 114 Hyperuricemia was defined as having SUA concentrations >7.0 mg/dL ($416.4\mu\text{mol/L}$) in men
5
6 115 or >6.0 mg/dL ($356.9\mu\text{mol/L}$) in women^{12, 13}. SUA levels were categorized into two groups
7
8 116 (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The
9
10 117 high SUA level group was classified as participants with hyperuricemia. BMI was defined as
11
12 118 weight divided by height² (kg/m^2) and categorized into two groups (non-obese [$< 28 \text{ kg/m}^2$] and
13
14 119 obese [$\geq 28 \text{ kg/m}^2$]) based on the Asia-Pacific criteria set by the World Health Organization^{14, 15}.
15
16 120 We excluded patients taken drugs that might affect uric acid metabolism, such as losartan,
17
18 121 furosemide, and allopurinol.

122 123 **Statistical analysis**

124 We conducted descriptive analysis to present the characteristics of baseline participants.
125 Continuous variables were reported as mean \pm standard deviation (SD) and categorical variables
126 as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese
127 and non-obese) were performed using Student's t-tests for continuous variables and Chi-
128 square analyses for categorical variables. Logistic regression model (LRM) was used to evaluate
129 the relationship between risk of obesity and risk factors for the data at baseline. We also utilized
130 generalized estimating equations (GEE) models with unstructured correlation structures to
131 quantify their longitudinal association between SUA and risk of obesity¹⁶, given the data on SUA
132 and obesity were repeatedly measured over the 9-year study period. All models were adjusted for
133 age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were
134 presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 $\mu\text{mol/L}$ or per-SD
135 increase in SUA.

136
137 We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age
138 group (youth <65 years vs. elderly ≥ 65 years). Additionally, we calculated the cut-off values of
139 SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria
140 including (1) the point on the curve with minimum distance from the left-upper corner of the unit

1
2
3
4 141 square; and (2) the point where the Youden's index is maximum¹⁷. A two-sided p-value less than
5
6 142 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3
7
8 143 (R Foundation for Statistical Computing, Vienna, Austria).

9
10 144

11 12 13 145 **Patient and public involvement**

14
15 146 There were no patient and/or public involvement in the design of this study. The IRB approved the
16
17 147 ethical waiver of informed consent for this study.

18
19
20 148

21 22 23 149 **Results**

24
25 150 There were 15,959 participants (10,023 males) included in this study. The average number of
26
27 151 health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD:
28
29 152 13.27) and a mean SUA of 367.05 $\mu\text{mol/L}$ (SD: 97.97) at baseline, respectively. There were 1,227
30
31 153 (7.6%) participants that were obese at baseline. Significant differences between the obese and
32
33 154 non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG,
34
35 155 BUN, and CR (p-value < 0.001) (**Table 1**). In total, the prevalence of obesity was approximately
36
37 156 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the
38
39 157 subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males
40
41 158 than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The
42
43 159 prevalence of obesity significantly increased with the number of medical checkup years in the
44
45 160 group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078
46
47 161 participants developed obesity over the 9-year period.

48
49
50 162

51
52 163 As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for
53
54 164 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
55
56 165 [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic
57
58 166 regression analysis (Model 1). When converted to categorical analysis, the risks of obesity were

1
2
3
4 167 greater among those with high level of SUA, males and younger participants. Likewise, with
5
6 168 longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2),
7
8 169 consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1
9
10 170 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
11
12 171 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by
13
14 172 categorical variables, we observed similar results with higher risk in male and elderly participants.

15
16 173

17
18 174 As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup
19
20 175 analyses. Significant associations between SUA and risk of obesity were observed, where female
21
22 176 [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an
23
24 177 elevated risk. To calculate the discrimination ability of SUA among obese participants at different
25
26 178 times of medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC
27
28 179 curves were calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area
29
30 180 under receiver operating curves (AUCs) of SUA in obesity participants stratified by gender. We
31
32 181 found that the overall cut-off values of SUA were 429.5 μ mol/L (range: 411.5-488.5 μ mol/L) in
33
34 182 males and 326.9 μ mol/L (range: 298.5-426.5 μ mol/L) in females when stratified by different times
35
36 183 of medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were
37
38 184 429.5 μ mol/L (range: 366.7-431.5 μ mol/L) in males and 326.9 μ mol/L (range: 301.5-362.1
39
40 185 μ mol/L) in females when stratified by different years of medical checkups.

41
42 186

43 44 45 187 **Discussion**

46
47
48 188 To the best of our knowledge, this is the first longitudinal study that estimated the relationship
49
50 189 between SUA and obesity over a long time period in China. The prevalence of obesity was
51
52 190 approximately 14.2% for high SUA level. Previous studies found that the prevalence of
53
54 191 hyperuricemia ranged from 2.5 to 25 % depending on the study population country¹⁸. For
55
56 192 instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand¹⁹,
57
58 193 ²⁰. Overall, we found high SUA level was associated with increased risk of obesity, within OR

1
2
3
4 194 value of 1.85 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with
5
6 195 prior studies ^{21,22}. Currently, obesity and hyperuricemia, as well as their associated health
7
8 196 complications (e.g. metabolic syndrome) have emerged as a major public health concern as a
9
10 197 result of the growing prevalence, and the estimated economic burden ⁷.

11
12 198

13
14
15 199 Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity,
16
17 200 suggesting the influence of overproduction and poor renal excretion ²³. Prior studies reported that
18
19 201 increased SUA level is closely related to excessive production of UA and the reduction of urinary
20
21 202 uric acid excretion and clearance ²⁴. This ultimately leads to increased risk of patients with
22
23 203 visceral fatty obesity ²³. Visceral fat accumulation (VFA) results in a large influx of plasma free
24
25 204 fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and
26
27 205 subsequently produced large amounts of UA through the activated UA synthesis pathway ^{25,26}.
28
29 206 Additionally, many researchers have reported a significant correlation between VFA and BMI ²⁷,
30
31 207 ²⁸. Therefore, because of the close biological relationship between UA and BMI, it is of great
32
33 208 importance for preventive medicine to pay attention to the interaction between UA and BMI.

34
35 209

36
37
38 210 Conflicting results regarding gender and age differences for the association between SUA and
39
40 211 obesity have been reported ^{10,29}. Our study found significant differences in obesity participants
41
42 212 with elevated OR value among high SUA level, male, and elderly for all medical checkup
43
44 213 participants. A similar study reported a positive relationship between BMI and SUA levels among
45
46 214 healthy individuals in China ³⁰. Nevertheless, in this study the subgroup analyses showed that
47
48 215 significant associated risk between SUA and obesity were observed higher in female and young
49
50 216 participants. This is consistent with a Thailand study that reported high SUA concentrations were
51
52 217 associated with greater risk of obesity in females ³¹. However, study in Bangladesh and Japan
53
54 218 reported that elevated SUA predicted obesity higher in males and the elderly^{8,29,31}. Perhaps the
55
56 219 associations of SUA with obesity varies by populations. Moreover, in a 10-year follow-up study,
57
58 220 BMI was observed to significantly increase with higher SUA levels regardless of race and gender

1
2
3
4 221 ³². Therefore, greater attention should be provided to those vulnerable populations in clinical
5
6 222 guidelines.
7

8
9 223

10
11 224 An important observation was that association between SUA and risk of obesity in the LRM
12
13 225 [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE
14
15 226 model [OR= (1.85 (1.77,1.91))] for 9-year all participants. The risk of obesity within
16
17 227 hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can
18
19 228 reflect the development of chronic diseases ³³. Regarding the assessment of cut-off values from
20
21 229 ROC of SUA in obesity participants, the cut-off values of SUA were 429.5 μ mol/L in males and
22
23 230 326.9 μ mol/L in females in stratified analysis by times or years of medical checkup. The cut-off
24
25 231 value was approximately consistent with the international standard for males ³⁴. However, it was
26
27 232 underestimated for women in the group of obese participants. Perhaps the proportion of females
28
29 233 were fewer in this study. The cut-off values for SUA in the study may be useful for distinguishing
30
31 234 tests among obesity and non-obesity participants, which were significant for certain risk value
32
33 235 prediction and guidance³⁵.

34
35 236

36
37 237 We must note several limitations in the present study. First, the underlying mechanism by which
38
39 238 SUA is increased in obese individuals remains not well understood. Second, this study did not
40
41 239 collect information on whether participants were prescribed medication to treat hyperuricemia.
42
43 240 Additionally, some medications used to treat hypertension may increase uric acid levels. Third,
44
45 241 there are numerous confounding factors that have not been considered, which can be studied
46
47 242 together with questionnaires in the future. Moreover, the younger screening population in this
48
49 243 study may underestimate the increased risk of uric acid among the elderly obese.

50
51
52 244

53
54 245 The present study has several strengths that must be noted. First, to our knowledge this is the first
55
56 246 large long-term medical checkup study to explore the relationship between SUA and obesity in
57
58 247 China. Second, the study analysis was based on the GEE model with high quality data by

1
2
3
4 248 controlling for confounding factors, which can increase the accuracy of the prediction. Third,
5
6 249 participants were representative of the general population with regard to clinical checkup and
7
8 250 obesity status, enhancing the generalizability of our findings. Moreover, results from this study
9
10 251 could inform prevention methods for obesity, especially in medically underserved areas where
11
12 252 medical service is insufficient.

13
14 253

15
16 254 This study filled current gaps in literature by analyzing the relationship between SUA and obesity
17
18 255 using medical checkup data. We observed that medical checkup data can be used to improve the
19
20 256 risk of obesity prediction accuracy. The medical checkup data used in this study can help provide
21
22 257 information that will facilitate intervention development and adoption at the individual level³⁶. The
23
24 258 utility of medical checkup data can potentially reach beyond predictive power alone in the near
25
26 259 future.

27
28
29 260

30 31 261 **Conclusions**

32
33
34 262 In conclusion, our study observed significant associations between SUA and obesity in this 9-year
35
36 263 longitudinal study. We mainly found higher SUA level was associated with increased risk of
37
38 264 obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the
39
40 265 number of medical checkup years in the group with high level of SUA. Additionally, the increased
41
42 266 risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses
43
44 267 revealed significant associations between SUA and obesity with higher risk for females and young
45
46 268 participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent
47
48 269 with the international standard. More evidence from well-designed studies are needed to confirm
49
50 270 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.

Competing interests: None declared.

Funding: Research grants from the Science Foundation of Guangdong Second Provincial General Hospital (YQ2019-008).

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.

Reference

1. Nagahama S, Kashino I, Hu H, Nanri A, Kurotani K, Kuwahara K *et al.* Haemoglobin A1c and hearing impairment: longitudinal analysis using a large occupational health check-up data of Japan. *BMJ open* 2018; **8**(9): e023220.
2. Kim YJ, Park H. Improving Prediction of High-Cost Health Care Users with Medical Check-Up Data. *Big data* 2019; **7**(3): 163-175.
3. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**(9995): 743-800.
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9945): 766-81.
5. Liu R, Han C, Wu D, Xia X, Gu J, Guan H *et al.* Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *BioMed research international* 2015; **2015**: 762820.
6. Ishizaka N, Ishizaka Y, Toda A, Tani M, Koike K, Yamakado M *et al.* Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. *The Journal of rheumatology* 2010; **37**(2): 410-6.
7. Chen MY, Zhao CC, Li TT, Zhu Y, Yu TP, Bao YQ *et al.* Serum uric acid levels are associated with obesity but not cardio-cerebrovascular events in Chinese inpatients with type 2 diabetes. *Scientific reports* 2017; **7**: 40009.
8. Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X *et al.* Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *European journal of epidemiology* 2013; **28**(8): 669-76.
9. Johnson RJ, Lanaspas MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. *Seminars in nephrology* 2011; **31**(5): 394-9.
10. Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. 2018; **13**(11): e0206850.
11. Yang C, Yang S, Feng C, Zhang C, Xu W, Zhang L *et al.* Associations of hyperuricemia and obesity with remission of nonalcoholic fatty liver disease among Chinese men: A retrospective cohort study. *PloS one* 2018; **13**(2): e0192396.
12. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic

- 1
2
3 syndrome in women and men. *Metabolism: clinical and experimental* 2008; **57**(6): 845-52.
4
5
6 13. You L, Liu A, Wuyun G, Wu H, Wang P. Prevalence of hyperuricemia and the relationship
7 between serum uric acid and metabolic syndrome in the Asian Mongolian area. *Journal of*
8 *atherosclerosis and thrombosis* 2014; **21**(4): 355-65.
9
10 14. WHO. Appropriate body-mass index for Asian populations and its implications for policy and
11 intervention strategies. *Lancet* 2004; **363**(9403): 157-63.
12
13 15. Li MF, Ren Y, Zhao CC, Zhang R, Li LX, Liu F *et al*. Prevalence and clinical characteristics of
14 lower limb atherosclerotic lesions in newly diagnosed patients with ketosis-onset diabetes: a
15 cross-sectional study. *Diabetology & metabolic syndrome* 2014; **6**: 71.
16
17 16. Buzkova P, Brown ER, John-Stewart GC. Longitudinal data analysis for generalized linear
18 models under participant-driven informative follow-up: an application in maternal health
19 epidemiology. *American journal of epidemiology* 2010; **171**(2): 189-97.
20
21 17. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off
22 value: the case of tests with continuous results. *Biochemia medica* 2016; **26**(3): 297-307.
23
24 18. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese.
25 *Obesity surgery* 2012; **22**(6): 945-8.
26
27 19. Uaratanawong S, Suraamornkul S, Angkeaw S, Uaratanawong R. Prevalence of hyperuricemia
28 in Bangkok population. *Clinical rheumatology* 2011; **30**(7): 887-93.
29
30 20. Ford DK, Demos AM. Serum Uric Acid Levels of Healthy Caucasian, Chinese and Haida Indian
31 Males in British Columbia. *Canadian Medical Association journal* 1964; **90**: 1295-7.
32
33 21. Kuwabara M, Kuwabara R, Hisatome I, Niwa K, Roncal-Jimenez CA, Bjornstad P *et al*.
34 "Metabolically Healthy" Obesity and Hyperuricemia Increase Risk for Hypertension and
35 Diabetes: 5-year Japanese Cohort Study. *Obesity* 2017; **25**(11): 1997-2008.
36
37 22. Zhang N, Chang Y, Guo X, Chen Y, Ye N, Sun Y. A Body Shape Index and Body Roundness
38 Index: Two new body indices for detecting association between obesity and hyperuricemia in
39 rural area of China. *European journal of internal medicine* 2016; **29**: 32-6.
40
41 23. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T *et al*. Effect of
42 visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity
43 is linked more closely to overproduction of uric acid than subcutaneous fat obesity.
44 *Metabolism: clinical and experimental* 1998; **47**(8): 929-33.
45
46 24. Han T, Meng X, Shan R, Zi T, Li Y, Ma H *et al*. Temporal relationship between hyperuricemia
47 and obesity, and its association with future risk of type 2 diabetes. *International journal of*
48 *obesity (2005)* 2018; **42**(7): 1336-1344.
49
50 25. Fabregat I, Revilla E, Machado A. Short-term control of the pentose phosphate cycle by
51 insulin could be modulated by the NADPH/NADP ratio in rat adipocytes and hepatocytes.
52 *Biochemical and biophysical research communications* 1987; **146**(2): 920-5.
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
26. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism: clinical and experimental* 1981; **30**(6): 616-34.
 27. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circulation journal : official journal of the Japanese Circulation Society* 2002; **66**(11): 987-92.
 28. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S *et al*. Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes research and clinical practice* 2009; **83**(1): 100-5.
 29. Tanaka K, Ogata S, Tanaka H, Omura K, Honda C, Hayakawa K. The relationship between body mass index and uric acid: a study on Japanese adult twins. *Environmental health and preventive medicine* 2015; **20**(5): 347-53.
 30. Wang H, Wang L, Xie R, Dai W, Gao C, Shen P *et al*. Association of Serum Uric Acid with Body Mass Index: A Cross-Sectional Study from Jiangsu Province, China. *Iranian journal of public health* 2014; **43**(11): 1503-9.
 31. Jaipakdee J, Jiamjarasrangsri W, Lohsoonthorn V, Lertmaharit S. Prevalence of metabolic syndrome and its association with serum uric acid levels in Bangkok Thailand. *The Southeast Asian journal of tropical medicine and public health* 2013; **44**(3): 512-22.
 32. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *European journal of epidemiology* 2007; **22**(7): 439-45.
 33. Nohara Y, Kai E. Health checkup and telemedical intervention program for preventive medicine in developing countries: verification study. 2015; **17**(1): e2.
 34. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Current opinion in rheumatology* 2014; **26**(2): 186-91.
 35. Mongioi LM, Condorelli RA, Barbagallo F, Cannarella R, La Vignera S, Calogero AE. Accuracy of the Low-Dose ACTH Stimulation Test for Adrenal Insufficiency Diagnosis: A Re-Assessment of the Cut-Off Value. *Journal of clinical medicine* 2019; **8**(6).
 36. Taninaga J, Nishiyama Y. Prediction of future gastric cancer risk using a machine learning algorithm and comprehensive medical check-up data: A case-control study. 2019; **9**(1): 12384.

1
2
3
4 **Tables and Figure legends:**

5 **Table 1.** Baseline characteristics and comparison between obesity and non-obesity participants.
6
7

8
9 **Table 2.** The prevalence of obesity by gender, age of checkup stratified by baseline SUA.
10
11

12
13 **Table 3.** Relationship between risk factors and risk of obesity in the models.
14
15

16 **Table 4.** Relationship between risk factors and risk of obesity in the models stratified by gender
17 and age group.
18
19

20
21
22 **Figure 1.** Location of Guangdong Second Provincial General Hospital (Guangzhou,
23 Guangdong, China) and the prevalence of obesity by different years stratified by baseline SUA.
24
25

26
27 **Figure 2.** Flow diagram showing selection process of participants in our study.
28
29

30
31
32
33
34 **Supplemental data:**

35
36
37 **Supplementary Figure 1.** The ROC curves showing the relationship between SUA and risk of
38 obesity stratified by gender and different times of medical checkups.
39
40

41
42 **Supplementary Figure 2.** The ROC curves showing the relationship between SUA and risk of
43 obesity stratified by gender and different years of medical checkups (from 2010 to 2018).
44
45
46
47
48
49
50
51
52
53
54

55
56 **Table 1.** Baseline characteristics and comparison between obesity and non-obesity participants.
57
58
59
60

Characteristics	All patients	Obesity ^a	Non-obesity	<i>p</i> -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/m².

^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.

^aObesity 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	
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

^dModel 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).

^eHigh 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.

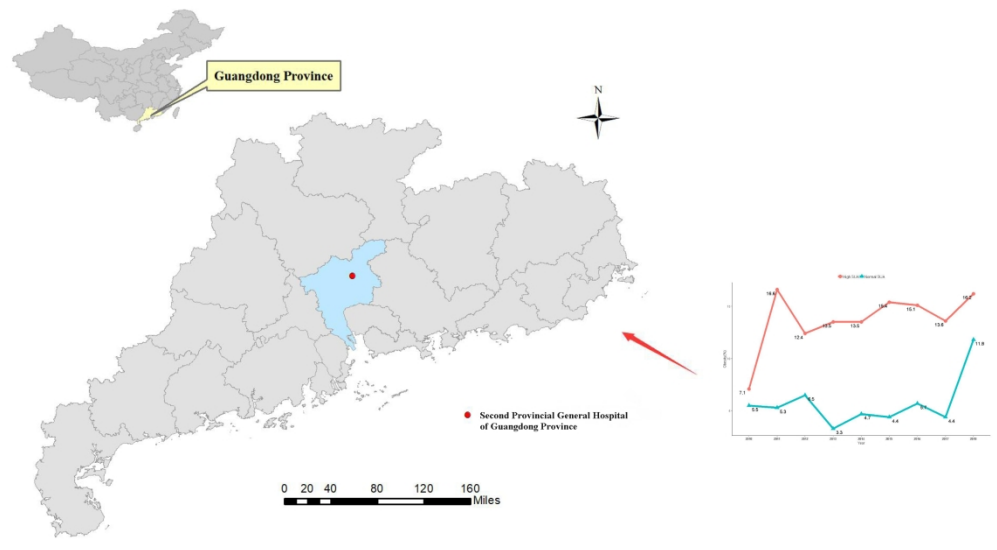
Variable	Generalized estimation equation model (GEE) ^c			
	Male		Female	
Gender	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
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)		
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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: ^aOR: odds ratio; ^bCI: confidence interval.

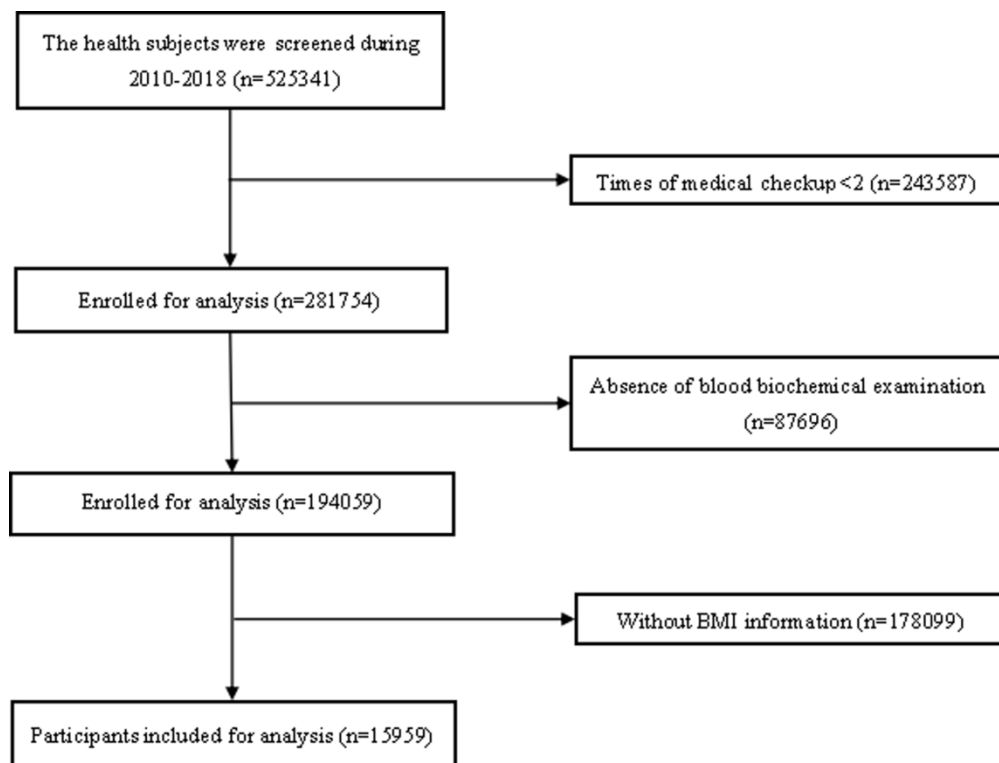
^cModel was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

^eHigh 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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

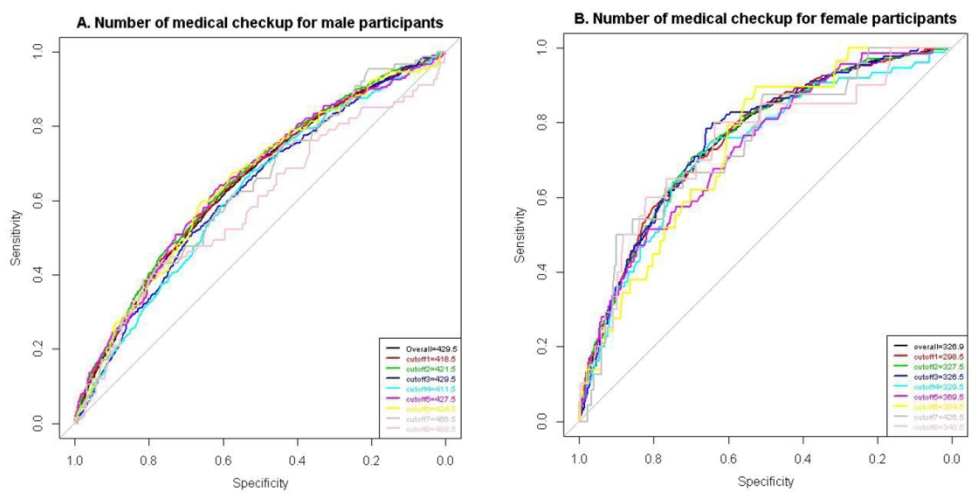


240x140mm (300 x 300 DPI)

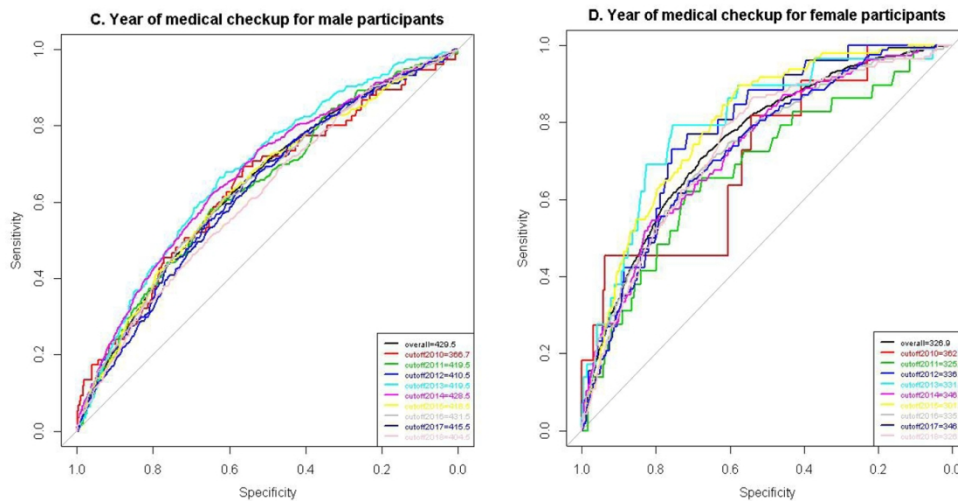


155x117mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



127x63mm (300 x 300 DPI)



127x64mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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

1			
2	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
3			
4			
5	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
6			
7			
8			
9			(b) Describe any methods used to examine subgroups and interactions
10			
11			(c) Explain how missing data were addressed
12			
13			(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
14			
15			
16			<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed
17			
18			
19			
20			<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy
21			
22			
23			(e) Describe any sensitivity analyses
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

Continued on next page

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	9-10
		<i>Cross-sectional study</i> —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
---------	----	---	----

1
2
3
4 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
5 unexposed groups in cohort and cross-sectional studies.
6
7
8

9
10 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
11 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
12 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
13 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
14 available at www.strobe-statement.org.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041919.R2
Article Type:	Original research
Date Submitted by the Author:	05-Oct-2020
Complete List of Authors:	Zeng, Jie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Lawrence, Wayne R; University at Albany State University of New York, Department of Epidemiology and Biostatistics Yang, Jun; Jinan University, Institute for Environmental and Climate Research Tian, Junzhang; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Cheng; Guangdong Second Provincial General Hospital, Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute Lian, Wanmin; Guangdong Second Provincial General Hospital, Center for Information He, Jingjun; Guangdong Second Provincial General Hospital, Center for Health Management and Examination Qu, Hongying; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Wang, Xiaojie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Liu, Hongmei; Guangdong Second Provincial General Hospital, Department of Ultrasound Li, Guanming; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Guowei; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Rheumatology, Public health
Keywords:	Public health < INFECTIOUS DISEASES, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 **Association between serum uric acid and obesity in Chinese adults: A**
5
6 **nine-year longitudinal data analysis**
7
8

9 Jie Zeng^{1,2}, Wayne R. Lawrence³, Jun Yang⁴, Junzhang Tian¹, Cheng Li⁵, Wanmin Lian⁶, Jingjun
10 He⁷, Hongying Qu^{1,7}, Xiaojie Wang¹, Hongmei Liu^{2,8}, Guanming Li^{1*}, and Guowei Li^{1,9*}
11
12

13
14 ¹ Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial
15 General Hospital, Guangzhou, China.
16

17 ² Institute of Ultrasound in Musculoskeletal Sports Medicine, Guangdong Second Provincial
18 General Hospital, Guangzhou, China.
19

20 ³ Department of Epidemiology and Biostatistics, School of Public Health, University at Albany,
21 State University of New York, One University Place, Rensselaer, New York.
22

23 ⁴ Institute for Environmental and Climate Research, Jinan University, Guangzhou, 511443, China.
24

25 ⁵ Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong
26 Second Provincial General Hospital, Guangzhou, China.
27

28 ⁶ Center for Information, Guangdong Second Provincial General Hospital, Guangzhou, China.
29

30 ⁷ Center for Health Management and Examination, Guangdong Second Provincial General Hospital,
31 Guangzhou, China.
32

33 ⁸ Department of Ultrasound, Guangdong Second Provincial General Hospital, Guangzhou, China.
34

35 ⁹ Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University,
36 Hamilton, ON, Canada.
37
38

39
40
41
42 ***Corresponding Authors:**

43 **Guowei Li, PhD**

44 CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.
45

46 Department of HEI, McMaster University, Hamilton, Canada L8S 4L8
47

48 Telephone: 86-020-89169025; Fax: 86-020-89168021
49

50 E-mail: liguowei099@126.com
51

52 and
53

54 **Guanming Li, MD**

55 CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.
56

57 Telephone: 86-020-32640264; Fax: 86-020-32640184
58
59

E-mail: lywergd@163.com

Word count: 2,953

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Abstract

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

6
7 **Methods:** Data were collected at Guangdong Second Provincial General Hospital in Guangzhou
8 City, China between January 2010 and December 2018. Participants with ≥ 2 medical checkup
9 times were included in our analyses. Physical examinations and laboratory measurement variables
10 were obtained from the medical checkup system. The high SUA level group was classified as
11 participants with hyperuricemia, and obesity was defined as $BMI \geq 28 \text{ kg/m}^2$. Logistic regression
12 model (LRM) was performed for data at baseline. For all participants, generalized estimation
13 equation (GEE) model was used to assess the association between SUA and obesity, where the
14 data were repeatedly measured over the nine-year study period. Subgroup analyses were
15 performed by gender and age group. We calculated the cut-off values for SUA of obesity using the
16 receiver operating characteristic curves (ROC) technique.

17
18 **Results:** A total of 15,959 participants (10,023 males and 5,936 females) were included in this
19 study, with an average age of 37.38 years (SD: 13.27) and average SUA of 367.05 $\mu\text{mol/L}$ (SD:
20 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year
21 period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic
22 regression analysis at baseline, we observed a positive association between SUA and risk of
23 obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated
24 measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95%
25 CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male (OR=1.45) and
26 elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant
27 associations between SUA and obesity with higher risk in female (OR=2.35) and young

1
2
3
4 28 participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48).

5
6 29 The SUA cut off points for risk of obesity using ROC curves were approximately consistent with
7
8 30 the international standard.
9

10 31

11
12
13 32 **Conclusions:** Our study observed higher SUA level was associated with increased risk of obesity.

14
15 33 More high-quality research is needed to further support these findings.
16

17 34

18
19
20 35 **Keywords:** serum uric acid, obesity, generalized estimation equation model, risk factors, China
21

22 36

23
24
25 37

26
27
28 38

29
30
31 39

32
33 40

34
35
36 41

37
38
39 42

40
41 43

42
43
44 44

45
46
47 45

48
49 46

50
51 47

52
53 48

54
55
56
57 49
58
59
60

1
2
3
4 50 **Strengths and limitations of this study**

5
6 51 ➤ This is the first large long-term medical checkup study to explore the relationship between
7
8 52 SUA and obesity in China.

9
10
11 53 ➤ The study analysis was based on the GEE model which can increase the accuracy of the
12
13 54 prediction.

14
15 55 ➤ The results from this study could inform prevention methods for obesity, especially in
16
17 56 medically underserved areas where medical service is insufficient.

18
19
20 57 ➤ The younger screening population in this study may underestimate the increased risk of uric
21
22 58 acid among the elderly obese.

23
24
25 59

26
27
28 60

61 Introduction

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

72
73 Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting
74 in hyperuricemia ^{3,4}. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and
75 7.9% for women ⁵. Additionally, in 2019 the obesity prevalence was nearing 12% in China.
76 Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was
77 reported to be independently correlated with changes in uric acid concentration, there might be an
78 interaction between them as suggested in prior pathophysiological and metabolic studies ⁶.
79 Epidemiological and clinical evidence supports a strong significant positive association between
80 SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq ⁷. A cross-
81 sectional study showed that body mass index (BMI) significantly increases with elevated SUA
82 among 27,009 middle-aged and elderly Chinese adults ⁸. Previous research showed that
83 hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis ⁹. With the
84 increasing prevalence of obesity among adults with hyperuricemia, it is of public health
85 importance to evaluate the long-term epidemiological transitions to develop policies centered on
86 intervention.

87

1
2
3
4 88 Numerous trend analyses have reported the association between SUA and BMI based on short-
5
6 89 term survey data in China ^{10, 11}. However, there remains a gap in evidence regarding the long-term
7
8 90 trend for providing estimates on the risks of obesity among Chinese adults during the last two
9
10 91 decades. Therefore, the present study aimed to examine the relationship between SUA and risk of
11
12 92 obesity using the 9-year medical checkup data among Chinese adults from 2010 to 2018.

13
14 93

16 94 **Methods**

17 95 **Study design and subjects**

18
19
20
21
22 96 We conducted a large retrospective study in China. Medical examinations were performed in 2010
23
24 97 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China
25
26 98 (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical
27
28 99 checkups; (2) absence of blood biochemical examination; and (3) no documented information on
29
30 100 BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).
31
32 101

33 34 35 102 **Measurements**

36
37 103 All participants were invited to join an in-person evaluation that included physical examination
38
39 104 and laboratory testing. Physical examinations were conducted following a standardized protocol,
40
41 105 including weight, height, waist circumference, hip circumference, and blood pressure. Waist
42
43 106 circumference was measured around the midway between the lowest border of the ribs and iliac
44
45 107 crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated
46
47 108 measurements in the presence of researchers. Laboratory measurements were obtained to measure
48
49 109 SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC),
50
51 110 triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C),
52
53 111 low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).
54
55 112

56 57 58 113 **Outcomes and definitions**

1
2
3
4 114 Hyperuricemia was defined as having SUA concentrations >7.0 mg/dL ($416.4\mu\text{mol/L}$) in men
5
6 115 or >6.0 mg/dL ($356.9\mu\text{mol/L}$) in women^{12, 13}. SUA levels were categorized into two groups
7
8 116 (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The
9
10 117 high SUA level group was classified as participants with hyperuricemia. BMI was defined as
11
12 118 weight divided by height² (kg/m^2) and categorized into two groups (non-obese [$< 28 \text{ kg/m}^2$] and
13
14 119 obese [$\geq 28 \text{ kg/m}^2$]) based on the Asia-Pacific criteria set by the World Health Organization^{14, 15}.
15
16 120 We excluded patients taken drugs that might affect uric acid metabolism, such as losartan,
17
18 121 furosemide, and allopurinol.

19
20 122

21 22 123 **Statistical analysis**

23
24
25 124 We conducted descriptive analysis to present the characteristics of baseline participants.
26
27 125 Continuous variables were reported as mean \pm standard deviation (SD) and categorical variables
28
29 126 as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese
30
31 127 and non-obese) were performed using Student's t-tests for continuous variables and Chi-
32
33 128 square analyses for categorical variables. Logistic regression model (LRM) was used to evaluate
34
35 129 the relationship between risk of obesity and risk factors for the data at baseline. We also utilized
36
37 130 generalized estimating equations (GEE) models with unstructured correlation structures to
38
39 131 quantify their longitudinal association between SUA and risk of obesity¹⁶, given the data on SUA
40
41 132 and obesity were repeatedly measured over the 9-year study period. All models were adjusted for
42
43 133 age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were
44
45 134 presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 $\mu\text{mol/L}$ or per-SD
46
47 135 increase in SUA.

48
49 136

50
51
52 137 We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age
53
54 138 group (youth <65 years vs. elderly ≥ 65 years). Additionally, we calculated the cut-off values of
55
56 139 SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria
57
58 140 including (1) the point on the curve with minimum distance from the left-upper corner of the unit

1
2
3
4 141 square; and (2) the point where the Youden's index is maximum¹⁷. A two-sided p-value less than
5
6 142 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3
7
8 143 (R Foundation for Statistical Computing, Vienna, Austria).
9

10 144

11 12 13 145 **Patient and public involvement**

14
15 146 There were no patient and/or public involvement in the design of this study.
16
17
18 147

19 20 21 148 **Results**

22
23 149 There were 15,959 participants (10,023 males) included in this study. The average number of
24
25 150 health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD:
26
27 151 13.27) and a mean SUA of 367.05 $\mu\text{mol/L}$ (SD: 97.97) at baseline, respectively. There were 1,227
28
29 152 (7.6%) participants that were obese at baseline. Significant differences between the obese and
30
31 153 non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG,
32
33 154 BUN, and CR (p-value < 0.001) (**Table 1**). In total, the prevalence of obesity was approximately
34
35 155 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the
36
37 156 subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males
38
39 157 than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The
40
41 158 prevalence of obesity significantly increased with the number of medical checkup years in the
42
43 159 group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078
44
45 160 participants developed obesity over the 9-year period.
46

47 161

48
49
50 162 As presented in **Table 3**, we observed at baseline significant differences on risk of obesity for
51
52 163 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
53
54 164 [OR=1.02 (95% CI:1.02,1.03)], and male gender [OR=1.27 (95% CI:1.16,1.39)] in the logistic
55
56 165 regression analysis (Model 1). When converted to categorical analysis, the risks of obesity were
57
58 166 greater among those with high level of SUA, males and younger participants. Likewise, with
59
60

1
2
3
4 167 longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2),
5
6 168 consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1
7
8 169 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
9
10 170 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by
11
12 171 categorical variables, we observed similar results with higher risk in male and elderly participants.
13
14 172

15
16
17 173 As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup
18
19 174 analyses. Significant associations between SUA and risk of obesity were observed, where female
20
21 175 [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an
22
23 176 elevated risk. We also did the analysis of baseline uric acid values vs obesity at the 9-year mark in
24
25 177 males and females, respectively where one eliminates baseline cases with hypertension, diabetes
26
27 178 or elevated BS, dyslipidemia, normal kidney function, baseline obesity. This result was consistent
28
29 179 with the subgroup analysis and well validate the data.
30
31 180

32
33
34 181 To calculate the discrimination ability of SUA among obese participants at different times of
35
36 182 medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were
37
38 183 calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver
39
40 184 operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the
41
42 185 overall cut-off values of SUA were 429.5 μ mol/L (range: 411.5-488.5 μ mol/L) in males and
43
44 186 326.9 μ mol/L (range: 298.5-426.5 μ mol/L) in females when stratified by different times of medical
45
46 187 checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5 μ mol/L
47
48 188 (range: 366.7-431.5 μ mol/L) in males and 326.9 μ mol/L (range: 301.5-362.1 μ mol/L) in females
49
50 189 when stratified by different years of medical checkups.
51

52 190

53 54 191 **Discussion**

55
56
57 192 To the best of our knowledge, this is the first longitudinal study that estimated the relationship
58
59
60

1
2
3
4 193 between SUA and obesity over a long time period in China. The prevalence of obesity was
5
6 194 approximately 14.2% for high SUA level. Previous studies found that the prevalence of
7
8 195 hyperuricemia ranged from 2.5 to 25 % depending on the study population country ¹⁸. For
9
10 196 instance, the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand ¹⁹,
11
12 197 ²⁰. Overall, we found high SUA level was associated with increased risk of obesity, within OR
13
14 198 value of 1.85 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with
15
16 199 prior studies ^{21,22}. Currently, obesity and hyperuricemia, as well as their associated health
17
18 200 complications (e.g. metabolic syndrome) have emerged as a major public health concern as a
19
20 201 result of the growing prevalence, and the estimated economic burden ⁷.

22

23
24 203 Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity,
25
26 204 suggesting the influence of overproduction and poor renal excretion ²³. Prior studies reported that
27
28 205 increased SUA level is closely related to excessive production of UA and the reduction of urinary
29
30 206 uric acid excretion and clearance ²⁴. This ultimately leads to increased risk of patients with
31
32 207 visceral fatty obesity ²³. Visceral fat accumulation (VFA) results in a large influx of plasma free
33
34 208 fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and
35
36 209 subsequently produced large amounts of UA through the activated UA synthesis pathway ^{25,26}.
37
38 210 Additionally, many researchers have reported a significant correlation between VFA and BMI ²⁷,
39
40 211 ²⁸. Therefore, because of the close biological relationship between UA and BMI, it is of great
41
42 212 importance for preventive medicine to pay attention to the interaction between UA and BMI.

44
45 213

46
47 214 Conflicting results regarding gender and age differences for the association between SUA and
48
49 215 obesity have been reported ^{10,29}. Our study found significant differences in obesity participants
50
51 216 with elevated OR value among high SUA level, male, and elderly for all medical checkup
52
53 217 participants. A similar study reported a positive relationship between BMI and SUA levels among
54
55 218 healthy individuals in China ³⁰. Nevertheless, in this study the subgroup analyses showed that
56
57 219 significant associated risk between SUA and obesity were observed higher in female and young

1
2
3
4 220 participants. This is consistent with a Thailand study that reported high SUA concentrations were
5
6 221 associated with greater risk of obesity in females³¹. However, study in Bangladesh and Japan
7
8 222 reported that elevated SUA predicted obesity higher in males and the elderly^{8,29,31}. Perhaps the
9
10 223 associations of SUA with obesity varies by populations. Moreover, in a 10-year follow-up study,
11
12 224 BMI was observed to significantly increase with higher SUA levels regardless of race and gender
13
14 225 ³². Therefore, greater attention should be provided to those vulnerable populations in clinical
15
16 226 guidelines.

17
18 227

19
20 228 An important observation was that association between SUA and risk of obesity in the LRM
21
22 229 [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE
23
24 230 model [OR= (1.85 (1.77,1.91))] for 9-year all participants. The risk of obesity within
25
26 231 hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can
27
28 232 reflect the development of chronic diseases³³. Regarding the assessment of cut-off values from
29
30 233 ROC of SUA in obesity participants, the cut-off values of SUA were 429.5 μ mol/L in males and
31
32 234 326.9 μ mol/L in females in stratified analysis by times or years of medical checkup. The cut-off
33
34 235 value was approximately consistent with the international standard for males³⁴. However, it was
35
36 236 underestimated for women in the group of obese participants. Perhaps the proportion of females
37
38 237 were fewer in this study. The cut-off values for SUA in the study may be useful for distinguishing
39
40 238 tests among obesity and non-obesity participants, which were significant for certain risk value
41
42 239 prediction and guidance³⁵.

43
44 240

45
46
47 241 We must note several limitations in the present study. First, the underlying mechanism by which
48
49 242 SUA is increased in obese individuals remains not well understood. Second, this study did not
50
51 243 collect information on whether participants were prescribed medication to treat hyperuricemia.
52
53 244 Additionally, some medications used to treat hypertension may increase uric acid levels. Third,
54
55 245 there are numerous confounding factors that have not been considered, which can be studied
56
57 246 together with questionnaires in the future. Moreover, the younger screening population in this

1
2
3
4 247 study may underestimate the increased risk of uric acid among the elderly obese.
5
6 248
7
8

9 249 The present study has several strengths that must be noted. First, to our knowledge this is the first
10 250 large long-term medical checkup study to explore the relationship between SUA and obesity in
11 251 China. Second, the study analysis was based on the GEE model with high quality data by
12 252 controlling for confounding factors, which can increase the accuracy of the prediction. Third,
13 253 participants were representative of the general population with regard to clinical checkup and
14 254 obesity status, enhancing the generalizability of our findings. Moreover, results from this study
15 255 could inform prevention methods for obesity, especially in medically underserved areas where
16 256 medical service is insufficient.
17
18
19
20
21
22
23
24
25 257

26
27
28 258 This study filled current gaps in literature by analyzing the relationship between SUA and obesity
29 259 using medical checkup data. We observed that medical checkup data can be used to improve the
30 260 risk of obesity prediction accuracy. The medical checkup data used in this study can help provide
31 261 information that will facilitate intervention development and adoption at the individual level³⁶. The
32 262 utility of medical checkup data can potentially reach beyond predictive power alone in the near
33 263 future.
34
35
36
37
38
39
40
41
42

43 265 **Conclusions**

44
45 266 In conclusion, our study observed significant associations between SUA and obesity in this 9-year
46 267 longitudinal study. We mainly found higher SUA level was associated with increased risk of
47 268 obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the
48 269 number of medical checkup years in the group with high level of SUA. Additionally, the increased
49 270 risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses
50 271 revealed significant associations between SUA and obesity with higher risk for females and young
51 272 participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent
52
53
54
55
56
57
58
59
60

1
2
3
4 273 with the international standard. More evidence from well-designed studies are needed to confirm
5
6 274 our findings.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

Funding:

Research grants from the Science Foundation of Guangdong Second Provincial General Hospital (YQ2019-008).

Reference

1. Nagahama S, Kashino I, Hu H, Nanri A, Kurotani K, Kuwahara K *et al.* Haemoglobin A1c and hearing impairment: longitudinal analysis using a large occupational health check-up data of Japan. *BMJ open* 2018; **8**(9): e023220.
2. Kim YJ, Park H. Improving Prediction of High-Cost Health Care Users with Medical Check-Up Data. *Big data* 2019; **7**(3): 163-175.
3. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**(9995): 743-800.
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9945): 766-81.
5. Liu R, Han C, Wu D, Xia X, Gu J, Guan H *et al.* Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *BioMed research international* 2015; **2015**: 762820.
6. Ishizaka N, Ishizaka Y, Toda A, Tani M, Koike K, Yamakado M *et al.* Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. *The Journal of rheumatology* 2010; **37**(2): 410-6.
7. Chen MY, Zhao CC, Li TT, Zhu Y, Yu TP, Bao YQ *et al.* Serum uric acid levels are associated with obesity but not cardio-cerebrovascular events in Chinese inpatients with type 2 diabetes. *Scientific reports* 2017; **7**: 40009.
8. Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X *et al.* Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *European journal of epidemiology* 2013; **28**(8): 669-76.
9. Johnson RJ, Lanaspas MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. *Seminars in nephrology* 2011; **31**(5): 394-9.
10. Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. 2018; **13**(11): e0206850.
11. Yang C, Yang S, Feng C, Zhang C, Xu W, Zhang L *et al.* Associations of hyperuricemia and obesity with remission of nonalcoholic fatty liver disease among Chinese men: A retrospective cohort study. *PloS one* 2018; **13**(2): e0192396.
12. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic

- 1
2
3 syndrome in women and men. *Metabolism: clinical and experimental* 2008; **57**(6): 845-52.
4
5
6 13. You L, Liu A, Wuyun G, Wu H, Wang P. Prevalence of hyperuricemia and the relationship
7 between serum uric acid and metabolic syndrome in the Asian Mongolian area. *Journal of*
8 *atherosclerosis and thrombosis* 2014; **21**(4): 355-65.
9
10 14. WHO. Appropriate body-mass index for Asian populations and its implications for policy and
11 intervention strategies. *Lancet* 2004; **363**(9403): 157-63.
12
13 15. Li MF, Ren Y, Zhao CC, Zhang R, Li LX, Liu F *et al*. Prevalence and clinical characteristics of
14 lower limb atherosclerotic lesions in newly diagnosed patients with ketosis-onset diabetes: a
15 cross-sectional study. *Diabetology & metabolic syndrome* 2014; **6**: 71.
16
17 16. Buzkova P, Brown ER, John-Stewart GC. Longitudinal data analysis for generalized linear
18 models under participant-driven informative follow-up: an application in maternal health
19 epidemiology. *American journal of epidemiology* 2010; **171**(2): 189-97.
20
21 17. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off
22 value: the case of tests with continuous results. *Biochemia medica* 2016; **26**(3): 297-307.
23
24 18. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese.
25 *Obesity surgery* 2012; **22**(6): 945-8.
26
27 19. Uaratanawong S, Suraamornkul S, Angkeaw S, Uaratanawong R. Prevalence of hyperuricemia
28 in Bangkok population. *Clinical rheumatology* 2011; **30**(7): 887-93.
29
30 20. Ford DK, Demos AM. Serum Uric Acid Levels of Healthy Caucasian, Chinese and Haida Indian
31 Males in British Columbia. *Canadian Medical Association journal* 1964; **90**: 1295-7.
32
33 21. Kuwabara M, Kuwabara R, Hisatome I, Niwa K, Roncal-Jimenez CA, Bjornstad P *et al*.
34 "Metabolically Healthy" Obesity and Hyperuricemia Increase Risk for Hypertension and
35 Diabetes: 5-year Japanese Cohort Study. *Obesity* 2017; **25**(11): 1997-2008.
36
37 22. Zhang N, Chang Y, Guo X, Chen Y, Ye N, Sun Y. A Body Shape Index and Body Roundness
38 Index: Two new body indices for detecting association between obesity and hyperuricemia in
39 rural area of China. *European journal of internal medicine* 2016; **29**: 32-6.
40
41 23. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T *et al*. Effect of
42 visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity
43 is linked more closely to overproduction of uric acid than subcutaneous fat obesity.
44 *Metabolism: clinical and experimental* 1998; **47**(8): 929-33.
45
46 24. Han T, Meng X, Shan R, Zi T, Li Y, Ma H *et al*. Temporal relationship between hyperuricemia
47 and obesity, and its association with future risk of type 2 diabetes. *International journal of*
48 *obesity (2005)* 2018; **42**(7): 1336-1344.
49
50 25. Fabregat I, Revilla E, Machado A. Short-term control of the pentose phosphate cycle by
51 insulin could be modulated by the NADPH/NADP ratio in rat adipocytes and hepatocytes.
52 *Biochemical and biophysical research communications* 1987; **146**(2): 920-5.
53
54
55
56
57
58
59
60

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
26. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism: clinical and experimental* 1981; **30**(6): 616-34.
27. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circulation journal : official journal of the Japanese Circulation Society* 2002; **66**(11): 987-92.
28. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S *et al.* Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes research and clinical practice* 2009; **83**(1): 100-5.
29. Tanaka K, Ogata S, Tanaka H, Omura K, Honda C, Hayakawa K. The relationship between body mass index and uric acid: a study on Japanese adult twins. *Environmental health and preventive medicine* 2015; **20**(5): 347-53.
30. Wang H, Wang L, Xie R, Dai W, Gao C, Shen P *et al.* Association of Serum Uric Acid with Body Mass Index: A Cross-Sectional Study from Jiangsu Province, China. *Iranian journal of public health* 2014; **43**(11): 1503-9.
31. Jaipakdee J, Jiamjarasrangsri W, Lohsoonthorn V, Lertmaharit S. Prevalence of metabolic syndrome and its association with serum uric acid levels in Bangkok Thailand. *The Southeast Asian journal of tropical medicine and public health* 2013; **44**(3): 512-22.
32. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *European journal of epidemiology* 2007; **22**(7): 439-45.
33. Nohara Y, Kai E. Health checkup and telemedical intervention program for preventive medicine in developing countries: verification study. 2015; **17**(1): e2.
34. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Current opinion in rheumatology* 2014; **26**(2): 186-91.
35. Mongioi LM, Condorelli RA, Barbagallo F, Cannarella R, La Vignera S, Calogero AE. Accuracy of the Low-Dose ACTH Stimulation Test for Adrenal Insufficiency Diagnosis: A Re-Assessment of the Cut-Off Value. *Journal of clinical medicine* 2019; **8**(6).
36. Taninaga J, Nishiyama Y. Prediction of future gastric cancer risk using a machine learning algorithm and comprehensive medical check-up data: A case-control study. 2019; **9**(1): 12384.

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	<i>p</i> -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/m².

^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.

^aObesity 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: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

^dModel 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).

^eHigh 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.

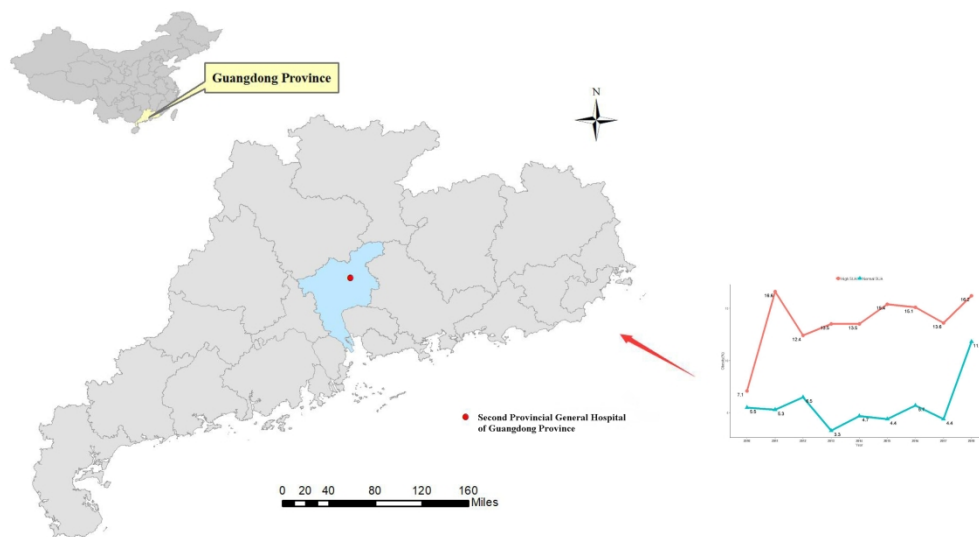
Variable	Generalized estimation equation model (GEE) ^c			
	Male		Female	
Gender	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
Continuous variable				
SUA (μmol/L)				
Per-1	1.01 (1.01,1.02)	<0.001	1.01 (1.01,1.02)	<0.001
Per-SD	1.70 (1.64,1.77)	<0.001	2.35 (2.16,2.55)	<0.001
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)		
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

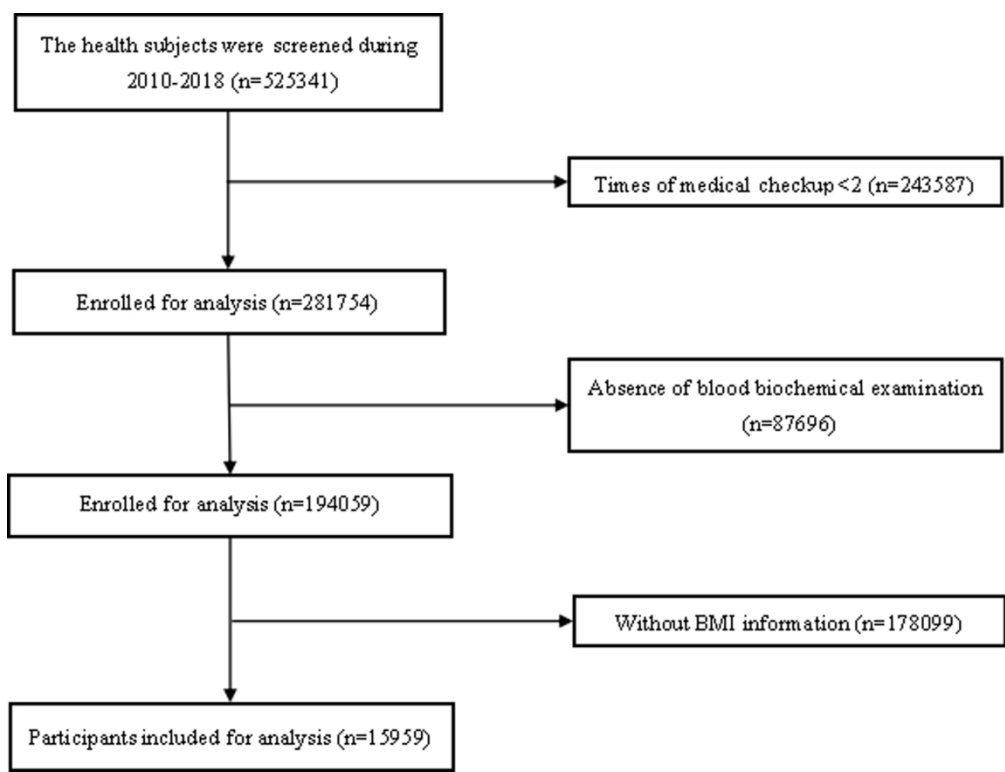
^eHigh SUA level was defined as the SUA greater than 420 mmol/L in men and greater than 360 mmol/L in women, while the others are normal.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

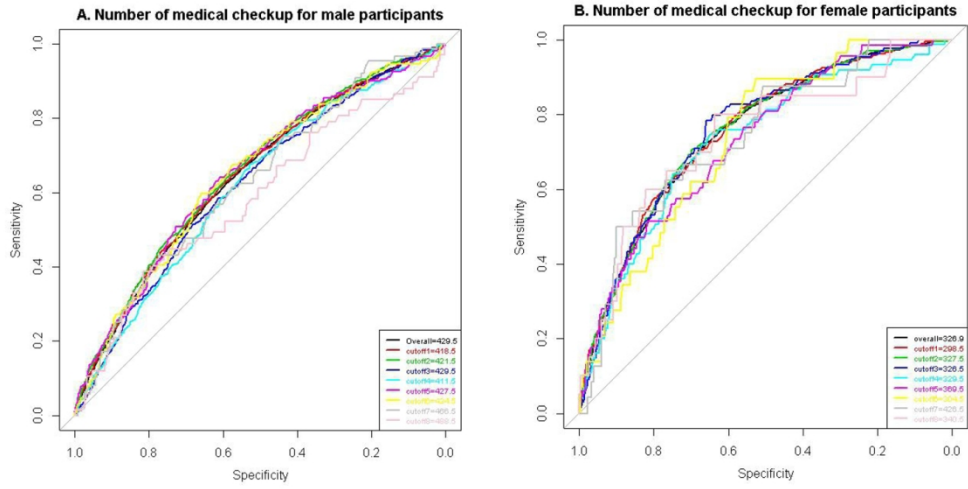


240x140mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

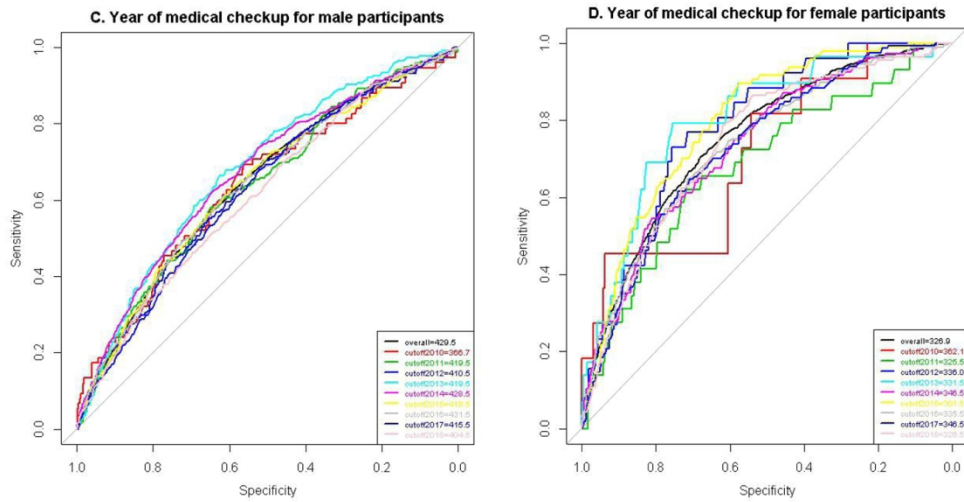


155x117mm (300 x 300 DPI)



127x63mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



127x64mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	8-9
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	8-9

Continued on next page

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	9-10
		<i>Cross-sectional study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

*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.

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041919.R3
Article Type:	Original research
Date Submitted by the Author:	06-Nov-2020
Complete List of Authors:	Zeng, Jie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Lawrence, Wayne R; University at Albany State University of New York, Department of Epidemiology and Biostatistics Yang, Jun; Jinan University, Institute for Environmental and Climate Research Tian, Junzhang; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Cheng; Guangdong Second Provincial General Hospital, Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute Lian, Wanmin; Guangdong Second Provincial General Hospital, Center for Information He, Jingjun; Guangdong Second Provincial General Hospital, Center for Health Management and Examination Qu, Hongying; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Wang, Xiaojie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Liu, Hongmei; Guangdong Second Provincial General Hospital, Department of Ultrasound Li, Guanming; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Guowei; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Rheumatology, Public health
Keywords:	Public health < INFECTIOUS DISEASES, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Jie Zeng^{1,2}, Wayne R. Lawrence³, Jun Yang⁴, Junzhang Tian¹, Cheng Li⁵, Wanmin Lian⁶, Jingjun He⁷, Hongying Qu^{1,7}, Xiaojie Wang¹, Hongmei Liu^{2,8}, Guanming Li^{1*}, and Guowei Li^{1,9*}

¹ Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, Guangzhou, China.

² Institute of Ultrasound in Musculoskeletal Sports Medicine, Guangdong Second Provincial General Hospital, Guangzhou, China.

³ Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, State University of New York, One University Place, Rensselaer, New York.

⁴ Institute for Environmental and Climate Research, Jinan University, Guangzhou, 511443, China.

⁵ Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁶ Center for Information, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁷ Center for Health Management and Examination, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁸ Department of Ultrasound, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁹ Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada.

*Corresponding Authors:

Guowei Li, PhD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Department of HEI, McMaster University, Hamilton, Canada L8S 4L8

Telephone: 86-020-89169025; Fax: 86-020-89168021

E-mail: liguowei099@126.com

and

Guanming Li, MD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Telephone: 86-020-32640264; Fax: 86-020-32640184

E-mail: lywergd@163.com

Word count: 2,953

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Abstract

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

6
7 **Methods:** Data were collected at Guangdong Second Provincial General Hospital in Guangzhou
8 City, China between January 2010 and December 2018. Participants with ≥ 2 medical checkup
9 times were included in our analyses. Physical examinations and laboratory measurement variables
10 were obtained from the medical checkup system. The high SUA level group was classified as
11 participants with hyperuricemia, and obesity was defined as $BMI \geq 28 \text{ kg/m}^2$. Logistic regression
12 model (LRM) was performed for data at baseline. For all participants, generalized estimation
13 equation (GEE) model was used to assess the association between SUA and obesity, where the
14 data were repeatedly measured over the nine-year study period. Subgroup analyses were
15 performed by gender and age group. We calculated the cut-off values for SUA of obesity using the
16 receiver operating characteristic curves (ROC) technique.

17
18 **Results:** A total of 15,959 participants (10,023 males and 5,936 females) were included in this
19 study, with an average age of 37.38 years (SD: 13.27) and average SUA of $367.05 \mu\text{mol/L}$ (SD:
20 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year
21 period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic
22 regression analysis at baseline, we observed a positive association between SUA and risk of
23 obesity: $OR=1.84$ (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated
24 measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95%
25 CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male ($OR=1.45$) and
26 elderly participants ($OR=1.01$). In subgroup analyses by gender and age, we observed significant
27 associations between SUA and obesity with higher risk in female ($OR=2.35$) and young

1
2
3
4 28 participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48).
5
6 29 The SUA cutoff points for risk of obesity using ROC curves were approximately consistent with
7
8 30 the international standard.
9

10 31

11
12
13 32 **Conclusions:** Our study observed higher SUA level was associated with increased risk of obesity.
14
15 33 More high-quality research is needed to further support these findings.
16

17 34

18
19
20 35 **Keywords:** serum uric acid, obesity, generalized estimation equation model, risk factors, China
21

22 36

23
24
25 37

26
27
28 38

29
30
31 39

32
33
34 40

35
36
37 41

38
39
40 42

41
42
43 43

44
45
46 44

47
48
49 45

50
51
52 46

53
54
55 47

56
57
58 48

59
60 49

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

50

51 **Strengths and limitations of this study**

52 ➤ This is the first large long-term medical checkup study to explore the relationship between
53 SUA and obesity in China.

54 ➤ The study analysis was based on the GEE model which can increase the accuracy of the
55 prediction.

56 ➤ The results from this study could inform prevention methods for obesity, especially in
57 medically underserved areas where medical service is insufficient.

58 ➤ The younger screening population in this study may underestimate the increased risk of uric
59 acid among the elderly obese.

60

61

62 Introduction

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

73
74 Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting
75 in hyperuricemia^{3,4}. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and
76 7.9% for women⁵. Additionally, in 2019 the obesity prevalence was nearing 12% in China.
77 Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was
78 reported to be independently correlated with changes in uric acid concentration, there might be an
79 interaction between them as suggested in prior pathophysiological and metabolic studies ⁶.
80 Epidemiological and clinical evidence supports a strong significant positive association between
81 SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq ⁷. A
82 cross-sectional study showed that body mass index (BMI) significantly increases with elevated
83 SUA among 27,009 middle-aged and elderly Chinese adults ⁸. Previous research showed that
84 hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis⁹. With the
85 increasing prevalence of obesity among adults with hyperuricemia, it is of public health
86 importance to evaluate the long-term epidemiological transitions to develop policies centered on
87 intervention.

88

1
2
3
4 89 Numerous trend analyses have reported the association between SUA and BMI based on
5
6 90 short-term survey data in China^{10, 11}. However, there remains a gap in evidence regarding the
7
8 91 long-term trend for providing estimates on the risks of obesity among Chinese adults during the
9
10 92 last two decades. Therefore, the present study aimed to examine the relationship between SUA
11
12 93 and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to
13
14 94 2018.

15 16 95 17 18 96 **Methods**

19 20 21 97 **Study design and subjects**

22
23
24 98 We conducted a large retrospective study in China. Medical examinations were performed in 2010
25
26 99 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China
27
28 100 (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical
29
30 101 checkups; (2) absence of blood biochemical examination; and (3) no documented information on
31
32 102 BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).
33
34 103

35 36 37 104 **Measurements**

38
39 105 All participants were invited to join an in-person evaluation that included physical examination
40
41 106 and laboratory testing. Physical examinations were conducted following a standardized protocol,
42
43 107 including weight, height, waist circumference, hip circumference, and blood pressure. Waist
44
45 108 circumference was measured around the midway between the lowest border of the ribs and iliac
46
47 109 crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated
48
49 110 measurements in the presence of researchers. Laboratory measurements were obtained to measure
50
51 111 SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC),
52
53 112 triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C),
54
55 113 low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).
56
57
58 114

115 **Outcomes and definitions**

116 Hyperuricemia was defined as having SUA concentrations >7.0 mg/dL ($416.4\mu\text{mol/L}$) in men
117 or >6.0 mg/dL ($356.9\mu\text{mol/L}$) in women^{12, 13}. SUA levels were categorized into two groups
118 (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The
119 high SUA level group was classified as participants with hyperuricemia. BMI was defined as
120 weight divided by height² (kg/m^2) and categorized into two groups (non-obese [$< 28 \text{ kg/m}^2$] and
121 obese [$\geq 28 \text{ kg/m}^2$]) based on the Asia-Pacific criteria set by the World Health Organization^{14, 15}.
122 We excluded patients taken drugs that might affect uric acid metabolism, such as losartan,
123 furosemide, and allopurinol.

125 **Statistical analysis**

126 We conducted descriptive analysis to present the characteristics of baseline participants.
127 Continuous variables were reported as mean \pm standard deviation (SD) and categorical variables
128 as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese
129 and non-obese) were performed using Student's t-tests for continuous variables and
130 Chi-square analyses for categorical variables. Logistic regression model (LRM) was used to
131 evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also
132 utilized generalized estimating equations (GEE) models with unstructured correlation structures to
133 quantify their longitudinal association between SUA and risk of obesity¹⁶, given the data on SUA
134 and obesity were repeatedly measured over the 9-year study period. All models were adjusted for
135 age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were
136 presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 $\mu\text{mol/L}$ or per-SD
137 increase in SUA.

138
139 We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age
140 group (youth <65 years vs. elderly ≥ 65 years). Additionally, we calculated the cut-off values of
141 SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria

1
2
3
4 142 including (1) the point on the curve with minimum distance from the left-upper corner of the unit
5
6 143 square; and (2) the point where the Youden's index is maximum¹⁷. A two-sided p-value less than
7
8 144 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3
9
10 145 (R Foundation for Statistical Computing, Vienna, Austria).

11
12 146

147 **Patient and public involvement**

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

149

150 **Results**

151 There were 15,959 participants (10,023 males) included in this study. The average number of
152 health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD:
153 13.27) and a mean SUA of 367.05 μmol/L (SD: 97.97) at baseline, respectively. There were 1,227
154 (7.6%) participants that were obese at baseline. Significant differences between the obese and
155 non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG,
156 BUN, and CR (p-value < 0.001) (**Table 1**). In total, the prevalence of obesity was approximately
157 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the
158 subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males
159 than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The
160 prevalence of obesity significantly increased with the number of medical checkup years in the
161 group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078
162 participants developed obesity over the 9-year period.

163

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

1
2
3
4 168 greater among those with high level of SUA, males and younger participants. Likewise, with
5
6 169 longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2),
7
8 170 consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1
9
10 171 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
11
12 172 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by
13
14 173 categorical variables, we observed similar results with higher risk in male and elderly participants.

15
16 174

17
18 175 As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup
19
20 176 analyses. Significant associations between SUA and risk of obesity were observed, where female
21
22 177 [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an
23
24 178 elevated risk. We also did the analysis of baseline uric acid values vs obesity at the 9-year mark in
25
26 179 males and females, respectively where one eliminates baseline cases with hypertension, diabetes
27
28 180 or elevated BS, dyslipidemia, normal kidney function, baseline obesity. This result was consistent
29
30 181 with the subgroup analysis and well validate the data.

31
32
33 182

34
35 183 To calculate the discrimination ability of SUA among obese participants at different times of
36
37 184 medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were
38
39 185 calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver
40
41 186 operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the
42
43 187 overall cut-off values of SUA were 429.5 μ mol/L (range: 411.5-488.5 μ mol/L) in males
44
45 188 and 326.9 μ mol/L (range: 298.5-426.5 μ mol/L) in females when stratified by different times of
46
47 189 medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5
48
49 190 μ mol/L (range: 366.7-431.5 μ mol/L) in males and 326.9 μ mol/L (range: 301.5-362.1 μ mol/L) in
50
51 191 females when stratified by different years of medical checkups.

52
53
54 192

55
56 193 **Discussion**

1
2
3
4 194 To the best of our knowledge, this is the first longitudinal study that estimated the relationship
5
6 195 between SUA and obesity over a long time period in China. The prevalence of obesity was
7
8 196 approximately 14.2% for high SUA level. Previous studies found that the prevalence of
9
10 197 hyperuricemia ranged from 2.5 to 25 % depending on the study population country ¹⁸.For instance,
11
12 198 the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand^{19, 20}. Overall,
13
14 199 we found high SUA level was associated with increased risk of obesity, within OR value of 1.85
15
16 200 (1.77,1.91) in the GEE model for all participants, which was nearly consistent with prior studies ²¹,
17
18 201 ²². Currently, obesity and hyperuricemia, as well as their associated health complications (e.g.
19
20 202 metabolic syndrome) have emerged as a major public health concern as a result of the growing
21
22 203 prevalence, and the estimated economic burden⁷.

204

205 Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity,
206 suggesting the influence of overproduction and poor renal excretion²³. Prior studies reported that
207 increased SUA level is closely related to excessive production of UA and the reduction of urinary
208 uric acid excretion and clearance ²⁴. This ultimately leads to increased risk of patients with
209 visceral fatty obesity²³. Visceral fat accumulation (VFA) results in a large influx of plasma free
210 fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and
211 subsequently produced large amounts of UA through the activated UA synthesis pathway^{25, 26}.
212 Additionally, many researchers have reported a significant correlation between VFA and BMI²⁷,
213 ²⁸. Therefore, because of the close biological relationship between UA and BMI, it is of great
214 importance for preventive medicine to pay attention to the interaction between UA and BMI.

215

216 Conflicting results regarding gender and age differences for the association between SUA and
217 obesity have been reported^{10, 29}.Our study found significant differences in obesity participants with
218 elevated OR value among high SUA level, male, and elderly for all medical checkup participants.
219 A similar study reported a positive relationship between BMI and SUA levels among healthy
220 individuals in China³⁰. Nevertheless, in this study the subgroup analyses showed that significant

1
2
3
4 221 associated risk between SUA and obesity were observed higher in female and young participants.
5
6 222 This is consistent with a Thailand study that reported high SUA concentrations were associated
7
8 223 with greater risk of obesity in females³¹. However, study in Bangladesh and Japan reported that
9
10 224 elevated SUA predicted obesity higher in males and the elderly^{8, 29, 31}. Perhaps the associations of
11
12 225 SUA with obesity varies by populations. Moreover, in a 10-year follow-up study, BMI was
13
14 226 observed to significantly increase with higher SUA levels regardless of race and gender ³².
15
16 227 Therefore, greater attention should be provided to those vulnerable populations in clinical
17
18 228 guidelines.

19
20 229

21
22 230 An important observation was that association between SUA and risk of obesity in the LRM
23
24 231 [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE
25
26 232 model [OR= (1.85 (1.77,1.91))] for 9-year all participants. The risk of obesity within
27
28 233 hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can
29
30 234 reflect the development of chronic diseases³³. Regarding the assessment of cut-off values from
31
32 235 ROC of SUA in obesity participants, the cut-off values of SUA were 429.5 μ mol/L in
33
34 236 males and 326.9 μ mol/L in females in stratified analysis by times or years of medical checkup. The
35
36 237 cut-off value was approximately consistent with the international standard for males³⁴. However, it
37
38 238 was underestimated for women in the group of obese participants. Perhaps the proportion of
39
40 239 females were fewer in this study. The cut-off values for SUA in the study may be useful for
41
42 240 distinguishing tests among obesity and non-obesity participants, which were significant for certain
43
44 241 risk value prediction and guidance³⁵.

45
46 242

47
48
49 243 To our knowledge, we must note several limitations in the present study. First, the underlying
50
51 244 mechanism by which SUA is increased in obese individuals remains not well understood. Second,
52
53 245 this study did not collect information on whether participants were prescribed medication to treat
54
55 246 hyperuricemia. Additionally, some medications used to treat hypertension may increase uric acid
56
57 247 levels. Third, there are numerous confounding factors that have not been considered, which can be

1
2
3
4 248 studied together with questionnaires in the future. Moreover, the younger screening population in
5 249 this study may underestimate the increased risk of uric acid among the elderly obese.

6
7
8 250

9
10 251 The present study has several strengths that must be noted. First, to our knowledge this is the first
11 252 large long-term medical checkup study to explore the relationship between SUA and obesity in
12 253 China. Second, the study analysis was based on the GEE model with high quality data by
13 254 controlling for confounding factors, which can increase the accuracy of the prediction. Third,
14 255 participants were representative of the general population with regard to clinical checkup and
15 256 obesity status, enhancing the generalizability of our findings. Moreover, results from this study
16 257 could inform prevention methods for obesity, especially in medically underserved areas where
17 258 medical service is insufficient.

18
19
20
21
22
23
24
25
26
27 259

28
29 260 This study filled current gaps in literature by analyzing the relationship between SUA and obesity
30 261 using medical checkup data. We observed that medical checkup data can be used to improve the
31 262 risk of obesity prediction accuracy. The medical checkup data used in this study can help provide
32 263 information that will facilitate intervention development and adoption at the individual level ³⁶.
33 264 The utility of medical checkup data can potentially reach beyond predictive power alone in the
34 265 near future.

35
36
37
38
39
40
41
42 266

43 44 267 **Conclusions**

45
46
47 268 In conclusion, our study observed significant associations between SUA and obesity in this 9-year
48 269 longitudinal study. We mainly found higher SUA level was associated with increased risk of
49 270 obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the
50 271 number of medical checkup years in the group with high level of SUA. Additionally, the increased
51 272 risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses
52 273 revealed significant associations between SUA and obesity with higher risk for females and young

1
2
3
4 274 participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent
5
6 275 with the international standard. More evidence from well-designed studies are needed to confirm
7
8 276 our findings.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

Funding:

Research grants from the Science Foundation of Guangdong Second Provincial General Hospital (YQ2019-008).

Reference

1. Nagahama S, Kashino I, Hu H, Nanri A, Kurotani K, Kuwahara K *et al*. Haemoglobin A1c and hearing impairment: longitudinal analysis using a large occupational health check-up data of Japan. *BMJ open* 2018; **8**(9): e023220.
2. Kim YJ, Park H. Improving Prediction of High-Cost Health Care Users with Medical Check-Up Data. *Big data* 2019; **7**(3): 163-175.
3. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**(9995): 743-800.
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9945): 766-81.
5. Liu R, Han C, Wu D, Xia X, Gu J, Guan H *et al*. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *BioMed research international* 2015; **2015**: 762820.
6. Ishizaka N, Ishizaka Y, Toda A, Tani M, Koike K, Yamakado M *et al*. Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. *The Journal of rheumatology* 2010; **37**(2): 410-6.
7. Chen MY, Zhao CC, Li TT, Zhu Y, Yu TP, Bao YQ *et al*. Serum uric acid levels are associated with obesity but not cardio-cerebrovascular events in Chinese inpatients with type 2 diabetes. *Scientific reports* 2017; **7**: 40009.
8. Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X *et al*. Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *European journal of epidemiology* 2013; **28**(8): 669-76.
9. Johnson RJ, Lanaspas MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. *Seminars in nephrology* 2011; **31**(5): 394-9.
10. Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. 2018; **13**(11): e0206850.
11. Yang C, Yang S, Feng C, Zhang C, Xu W, Zhang L *et al*. Associations of hyperuricemia and obesity with remission of nonalcoholic fatty liver disease among Chinese men: A retrospective cohort study. *PloS one* 2018; **13**(2): e0192396.
12. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic

- 1
2
3 syndrome in women and men. *Metabolism: clinical and experimental* 2008; **57**(6): 845-52.
4
5
6 13. You L, Liu A, Wuyun G, Wu H, Wang P. Prevalence of hyperuricemia and the relationship
7 between serum uric acid and metabolic syndrome in the Asian Mongolian area. *Journal of*
8 *atherosclerosis and thrombosis* 2014; **21**(4): 355-65.
9
10 14. WHO. Appropriate body-mass index for Asian populations and its implications for policy and
11 intervention strategies. *Lancet* 2004; **363**(9403): 157-63.
12
13 15. Li MF, Ren Y, Zhao CC, Zhang R, Li LX, Liu F *et al.* Prevalence and clinical characteristics of
14 lower limb atherosclerotic lesions in newly diagnosed patients with ketosis-onset diabetes: a
15 cross-sectional study. *Diabetology & metabolic syndrome* 2014; **6**: 71.
16
17 16. Buzkova P, Brown ER, John-Stewart GC. Longitudinal data analysis for generalized linear
18 models under participant-driven informative follow-up: an application in maternal health
19 epidemiology. *American journal of epidemiology* 2010; **171**(2): 189-97.
20
21 17. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off
22 value: the case of tests with continuous results. *Biochemia medica* 2016; **26**(3): 297-307.
23
24 18. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese.
25 *Obesity surgery* 2012; **22**(6): 945-8.
26
27 19. Uaratanawong S, Suraamornkul S, Angkeaw S, Uaratanawong R. Prevalence of hyperuricemia
28 in Bangkok population. *Clinical rheumatology* 2011; **30**(7): 887-93.
29
30 20. Ford DK, Demos AM. Serum Uric Acid Levels of Healthy Caucasian, Chinese and Haida Indian
31 Males in British Columbia. *Canadian Medical Association journal* 1964; **90**: 1295-7.
32
33 21. Kuwabara M, Kuwabara R, Hisatome I, Niwa K, Roncal-Jimenez CA, Bjornstad P *et*
34 *al.* "Metabolically Healthy" Obesity and Hyperuricemia Increase Risk for Hypertension and
35 Diabetes: 5-year Japanese Cohort Study. *Obesity* 2017; **25**(11): 1997-2008.
36
37 22. Zhang N, Chang Y, Guo X, Chen Y, Ye N, Sun Y. A Body Shape Index and Body Roundness
38 Index: Two new body indices for detecting association between obesity and hyperuricemia in
39 rural area of China. *European journal of internal medicine* 2016; **29**: 32-6.
40
41 23. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T *et al.* Effect of
42 visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity
43 is linked more closely to overproduction of uric acid than subcutaneous fat obesity.
44 *Metabolism: clinical and experimental* 1998; **47**(8): 929-33.
45
46 24. Han T, Meng X, Shan R, Zi T, Li Y, Ma H *et al.* Temporal relationship between hyperuricemia
47 and obesity, and its association with future risk of type 2 diabetes. *International journal of*
48 *obesity (2005)* 2018; **42**(7): 1336-1344.
49
50 25. Fabregat I, Revilla E, Machado A. Short-term control of the pentose phosphate cycle by
51 insulin could be modulated by the NADPH/NADP ratio in rat adipocytes and hepatocytes.
52 *Biochemical and biophysical research communications* 1987; **146**(2): 920-5.
53
54
55
56
57
58
59
60

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
26. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism: clinical and experimental* 1981; **30**(6): 616-34.
27. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circulation journal : official journal of the Japanese Circulation Society* 2002; **66**(11): 987-92.
28. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S *et al*. Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes research and clinical practice* 2009; **83**(1): 100-5.
29. Tanaka K, Ogata S, Tanaka H, Omura K, Honda C, Hayakawa K. The relationship between body mass index and uric acid: a study on Japanese adult twins. *Environmental health and preventive medicine* 2015; **20**(5): 347-53.
30. Wang H, Wang L, Xie R, Dai W, Gao C, Shen P *et al*. Association of Serum Uric Acid with Body Mass Index: A Cross-Sectional Study from Jiangsu Province, China. *Iranian journal of public health* 2014; **43**(11): 1503-9.
31. Jaipakdee J, Jiamjarasrangsri W, Lohsoonthorn V, Lertmaharit S. Prevalence of metabolic syndrome and its association with serum uric acid levels in Bangkok Thailand. *The Southeast Asian journal of tropical medicine and public health* 2013; **44**(3): 512-22.
32. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *European journal of epidemiology* 2007; **22**(7): 439-45.
33. Nohara Y, Kai E. Health checkup and telemedical intervention program for preventive medicine in developing countries: verification study. 2015; **17**(1): e2.
34. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Current opinion in rheumatology* 2014; **26**(2): 186-91.
35. Mongioi LM, Condorelli RA, Barbagallo F, Cannarella R, La Vignera S, Calogero AE. Accuracy of the Low-Dose ACTH Stimulation Test for Adrenal Insufficiency Diagnosis: A Re-Assessment of the Cut-Off Value. *Journal of clinical medicine* 2019; **8**(6).
36. Taninaga J, Nishiyama Y. Prediction of future gastric cancer risk using a machine learning algorithm and comprehensive medical check-up data: A case-control study. 2019; **9**(1): 12384.

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	<i>p</i> -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.

^aObesity was defined as body mass index (BMI) ≥ 28.0 kg/m².

^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

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.

^aObesity 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: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

^dModel 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).

^eHigh 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			
	Male		Female	
Gender	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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)	
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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: ^aOR: odds ratio; ^bCI: confidence interval.

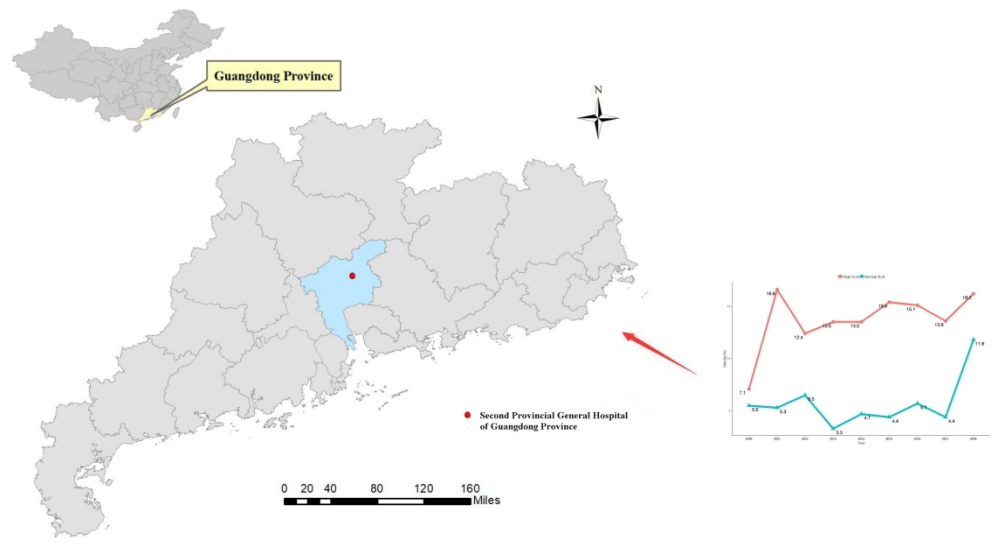
^cModel was adjusted for the variables of repeated times or years of medical checkup, age, sex, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, CR based on all medical checkup participants by using generalized estimation equation model (GEE).

^eHigh 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.

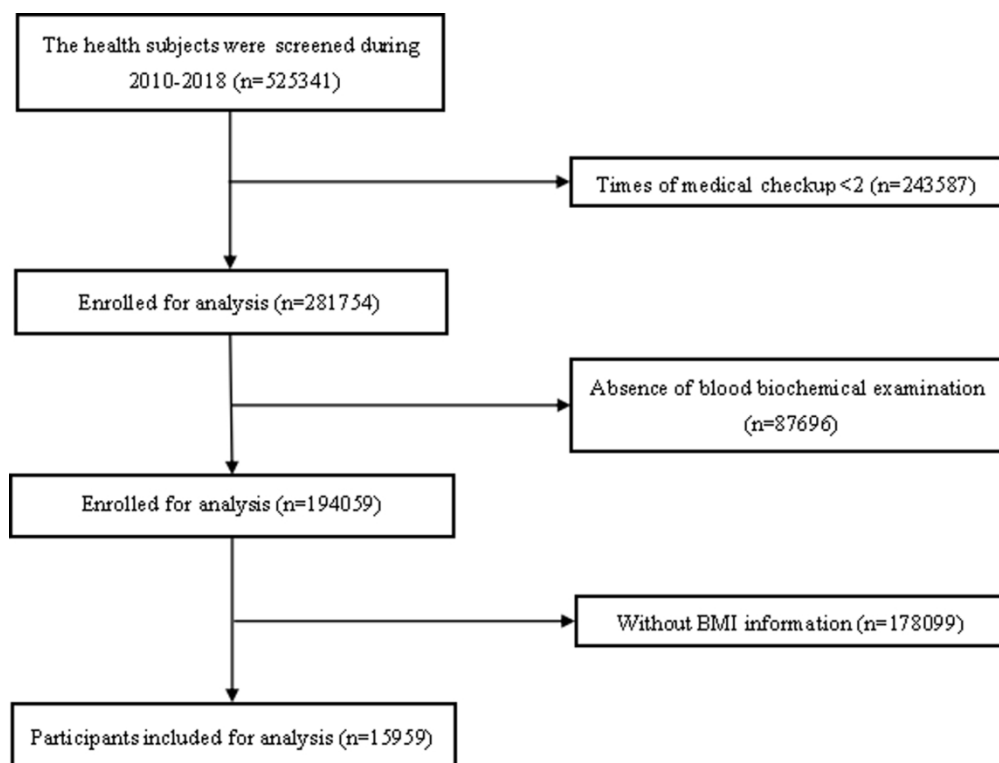
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

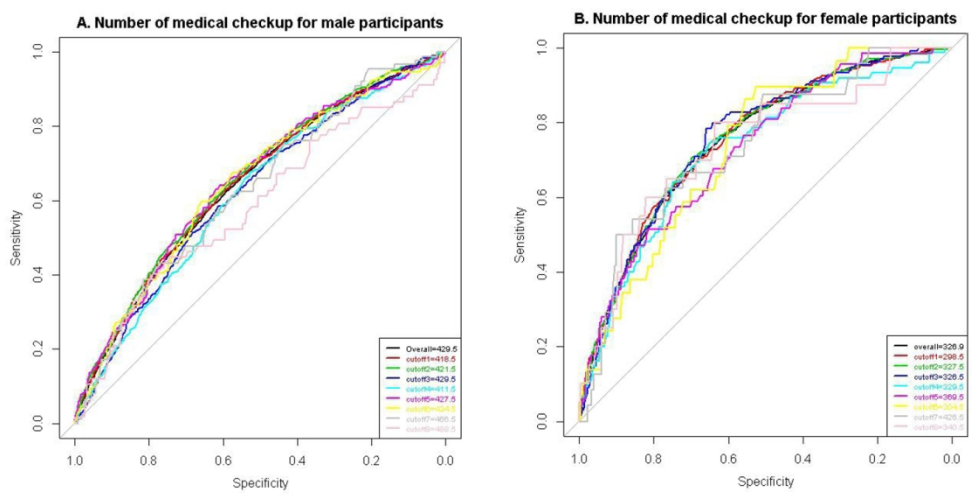


240x140mm (300 x 300 DPI)

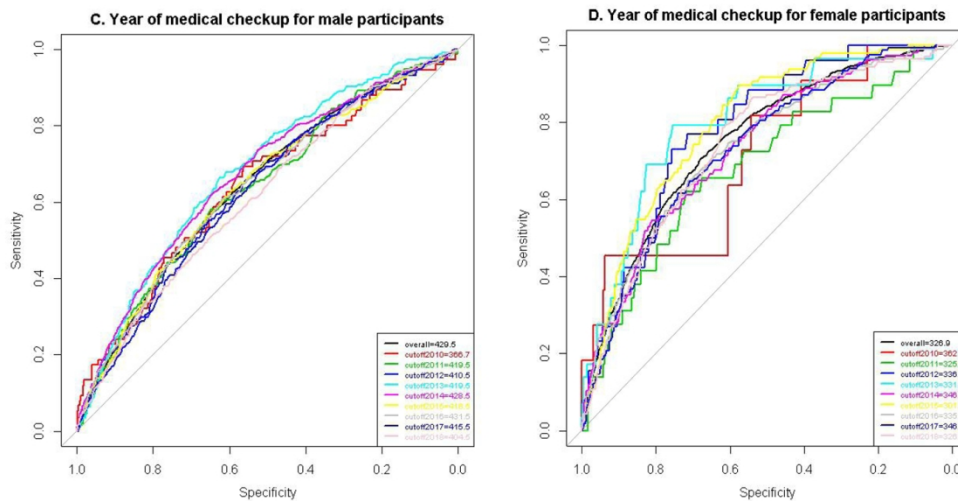


155x117mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



127x63mm (300 x 300 DPI)



127x64mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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

1			
2	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
3			
4			
5	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
6			
7			
8			
9			(b) Describe any methods used to examine subgroups and interactions
10			
11			(c) Explain how missing data were addressed
12			
13			(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
14			
15			
16			<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed
17			
18			
19			
20			<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy
21			
22			
23			(e) Describe any sensitivity analyses
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

Continued on next page

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	9-10
		<i>Cross-sectional study</i> —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

1
2
3
4 *Give information separately for cases and controls in case-control studies and, if applicable, for exposed and
5 unexposed groups in cohort and cross-sectional studies.
6
7
8

9
10 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
11 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
12 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
13 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
14 available at www.strobe-statement.org.
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041919.R4
Article Type:	Original research
Date Submitted by the Author:	14-Nov-2020
Complete List of Authors:	Zeng, Jie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Lawrence, Wayne R; University at Albany State University of New York, Department of Epidemiology and Biostatistics Yang, Jun; Jinan University, Institute for Environmental and Climate Research Tian, Junzhang; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Cheng; Guangdong Second Provincial General Hospital, Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute Lian, Wanmin; Guangdong Second Provincial General Hospital, Center for Information He, Jingjun; Guangdong Second Provincial General Hospital, Center for Health Management and Examination Qu, Hongying; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Wang, Xiaojie; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Liu, Hongmei; Guangdong Second Provincial General Hospital, Department of Ultrasound Li, Guanming; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology Li, Guowei; Guangdong Second Provincial General Hospital, Center for Clinical Epidemiology and Methodology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Rheumatology, Public health
Keywords:	Public health < INFECTIOUS DISEASES, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Epidemiology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Jie Zeng^{1,2}, Wayne R. Lawrence³, Jun Yang⁴, Junzhang Tian¹, Cheng Li⁵, Wanmin Lian⁶, Jingjun He⁷, Hongying Qu^{1,7}, Xiaojie Wang¹, Hongmei Liu^{2,8}, Guanming Li^{1*}, and Guowei Li^{1,9*}

¹ Center for Clinical Epidemiology and Methodology (CCEM), Guangdong Second Provincial General Hospital, Guangzhou, China.

² Institute of Ultrasound in Musculoskeletal Sports Medicine, Guangdong Second Provincial General Hospital, Guangzhou, China.

³ Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, State University of New York, One University Place, Rensselaer, New York.

⁴ Institute for Environmental and Climate Research, Jinan University, Guangzhou, 511443, China.

⁵ Guangdong Traditional Medical and Sports Injury Rehabilitation Research Institute, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁶ Center for Information, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁷ Center for Health Management and Examination, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁸ Department of Ultrasound, Guangdong Second Provincial General Hospital, Guangzhou, China.

⁹ Department of Health Research Methods, Evidence, and Impact (HEI), McMaster University, Hamilton, ON, Canada.

*Corresponding Authors:

Guowei Li, PhD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Department of HEI, McMaster University, Hamilton, Canada L8S 4L8

Telephone: 86-020-89169025; Fax: 86-020-89168021

E-mail: liguowei099@126.com

and

Guanming Li, MD

CCEM, Guangdong Second Provincial General Hospital, Guangzhou 510317, China.

Telephone: 86-020-32640264; Fax: 86-020-32640184

E-mail: lywergd@163.com

Word count: 2,953

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Abstract

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

6
7 **Methods:** Data were collected at Guangdong Second Provincial General Hospital in Guangzhou
8 City, China between January 2010 and December 2018. Participants with ≥ 2 medical checkup
9 times were included in our analyses. Physical examinations and laboratory measurement variables
10 were obtained from the medical checkup system. The high SUA level group was classified as
11 participants with hyperuricemia, and obesity was defined as $BMI \geq 28 \text{ kg/m}^2$. Logistic regression
12 model (LRM) was performed for data at baseline. For all participants, generalized estimation
13 equation (GEE) model was used to assess the association between SUA and obesity, where the
14 data were repeatedly measured over the nine-year study period. Subgroup analyses were
15 performed by gender and age group. We calculated the cut-off values for SUA of obesity using the
16 receiver operating characteristic curves (ROC) technique.

17
18 **Results:** A total of 15,959 participants (10,023 males and 5,936 females) were included in this
19 study, with an average age of 37.38 years (SD: 13.27) and average SUA of $367.05 \mu\text{mol/L}$ (SD:
20 97.97) at baseline, respectively. Finally, 1078 participants developed obesity over the 9-year
21 period. The prevalence of obesity was approximately 14.2% for high SUA level. In logistic
22 regression analysis at baseline, we observed a positive association between SUA and risk of
23 obesity: OR=1.84 (95% CI: 1.77,1.90) for per-SD increase in SUA. Considering repeated
24 measures over 9-year for all participants in the GEE model, the per-SD OR was 1.85 (95%
25 CI:1.77,1.91) for SUA and the increased risk of obesity were greater for male (OR=1.45) and
26 elderly participants (OR=1.01). In subgroup analyses by gender and age, we observed significant
27 associations between SUA and obesity with higher risk in female (OR=2.35) and young

1
2
3
4 28 participants (OR=1.87) when compared to male (OR=1.70) and elderly participants (OR=1.48).

5
6 29 The SUA cutoff points for risk of obesity using ROC curves were approximately consistent with
7
8 30 the international standard.
9

10 31

11
12
13 32 **Conclusions:** Our study observed higher SUA level was associated with increased risk of obesity.

14
15 33 More high-quality research is needed to further support these findings.
16

17 34

18
19
20 35 **Keywords:** serum uric acid, obesity, generalized estimation equation model, risk factors, China
21

22 36

23
24
25 37

26
27
28 38

29
30
31 39

32
33 40

34
35
36 41

37
38
39 42

40
41 43

42
43
44 44

45
46
47 45

48
49 46

50
51 47

52
53 48

54
55
56
57 49
58
59
60

1
2
3
4 50
56 51 **Strengths and limitations of this study**
78
9 52 ➤ This is the first large long-term medical checkup study to explore the relationship between
10
11 53 SUA and obesity in China.12
13 54 ➤ The study analysis was based on the GEE model which can increase the accuracy of the
14
15 55 prediction.16
17
18 56 ➤ The results from this study could inform prevention methods for obesity, especially in
19
20 57 medically underserved areas where medical service is insufficient.21
22 58 ➤ The younger screening population in this study may underestimate the increased risk of uric
23
24 59 acid among the elderly obese.
2526
27 60
28
2930 61
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

62 Introduction

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

73
74 Serum uric acid (SUA) is the final product of purine metabolism in humans, potentially resulting
75 in hyperuricemia^{3,4}. In China, the prevalence of hyperuricemia is 13.3%, with 19.4% for men and
76 7.9% for women⁵. Additionally, in 2019 the obesity prevalence was nearing 12% in China.
77 Among obese patients, hyperuricemia is commonly observed. Although changes in obesity was
78 reported to be independently correlated with changes in uric acid concentration, there might be an
79 interaction between them as suggested in prior pathophysiological and metabolic studies ⁶.
80 Epidemiological and clinical evidence supports a strong significant positive association between
81 SUA and obesity in the adult population of China, Japan, India, Pakistan, and Iraq ⁷. A
82 cross-sectional study showed that body mass index (BMI) significantly increases with elevated
83 SUA among 27,009 middle-aged and elderly Chinese adults ⁸. Previous research showed that
84 hyperuricemia can cause obesity by accelerating hepatic and peripheral lipogenesis⁹. With the
85 increasing prevalence of obesity among adults with hyperuricemia, it is of public health
86 importance to evaluate the long-term epidemiological transitions to develop policies centered on
87 intervention.

88

1
2
3
4 89 Numerous trend analyses have reported the association between SUA and BMI based on
5
6 90 short-term survey data in China^{10, 11}. However, there remains a gap in evidence regarding the
7
8 91 long-term trend for providing estimates on the risks of obesity among Chinese adults during the
9
10 92 last two decades. Therefore, the present study aimed to examine the relationship between SUA
11
12 93 and risk of obesity using the 9-year medical checkup data among Chinese adults from 2010 to
13
14 94 2018.

15
16 95

18 96 **Methods**

21 97 **Study design and subjects**

23
24 98 We conducted a large retrospective study in China. Medical examinations were performed in 2010
25
26 99 and 2018 at the Guangdong Second Provincial General Hospital in Guangzhou City, China
27
28 100 (**Figure 1**). Individuals were excluded from the study due to having (1) less than two medical
29
30 101 checkups; (2) absence of blood biochemical examination; and (3) no documented information on
31
32 102 BMI. Thus, a total of 15,959 participants were included in the study analysis (**Figure 2**).

33
34 103

37 104 **Measurements**

39
40 105 All participants were invited to join an in-person evaluation that included physical examination
41
42 106 and laboratory testing. Physical examinations were conducted following a standardized protocol,
43
44 107 including weight, height, waist circumference, hip circumference, and blood pressure. Waist
45
46 108 circumference was measured around the midway between the lowest border of the ribs and iliac
47
48 109 crest in the horizontal plane. The quality of anthropometric data was confirmed by repeated
49
50 110 measurements in the presence of researchers. Laboratory measurements were obtained to measure
51
52 111 SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC),
53
54 112 triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C),
55
56 113 low-density lipoprotein cholesterol (LDL-C), creatinine (Cr) and blood urea nitrogen (BUN).

57
58 114

115 **Outcomes and definitions**

116 Hyperuricemia was defined as having SUA concentrations >7.0 mg/dL ($416.4\mu\text{mol/L}$) in men
117 or >6.0 mg/dL ($356.9\mu\text{mol/L}$) in women^{12, 13}. SUA levels were categorized into two groups
118 (normal and high SUA) to compare the prevalence of obesity and its association with SUA. The
119 high SUA level group was classified as participants with hyperuricemia. BMI was defined as
120 weight divided by height² (kg/m^2) and categorized into two groups (non-obese [$< 28 \text{ kg/m}^2$] and
121 obese [$\geq 28 \text{ kg/m}^2$]) based on the Asia-Pacific criteria set by the World Health Organization^{14, 15}.
122 We excluded patients taken drugs that might affect uric acid metabolism, such as losartan,
123 furosemide, and allopurinol.

125 **Statistical analysis**

126 We conducted descriptive analysis to present the characteristics of baseline participants.
127 Continuous variables were reported as mean \pm standard deviation (SD) and categorical variables
128 as frequency and percentage, unless otherwise specified. Comparisons between two groups (obese
129 and non-obese) were performed using Student's t-tests for continuous variables and
130 Chi-square analyses for categorical variables. Logistic regression model (LRM) was used to
131 evaluate the relationship between risk of obesity and risk factors for the data at baseline. We also
132 utilized generalized estimating equations (GEE) models with unstructured correlation structures to
133 quantify their longitudinal association between SUA and risk of obesity¹⁶, given the data on SUA
134 and obesity were repeatedly measured over the 9-year study period. All models were adjusted for
135 age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG, BUN, and CR in each group. Results were
136 presented as odds ratio (OR) and 95% confidence interval (CI) with per-1 $\mu\text{mol/L}$ or per-SD
137 increase in SUA.

138
139 We performed subgroup analyses using GEE models by: 1) gender (male vs female); and 2) age
140 group (youth <65 years vs. elderly ≥ 65 years). Additionally, we calculated the cut-off values of
141 SUA for risk of obesity using the receiver operating characteristic (ROC) curves, based on criteria

1
2
3
4 142 including (1) the point on the curve with minimum distance from the left-upper corner of the unit
5
6 143 square; and (2) the point where the Youden's index is maximum¹⁷. A two-sided p-value less than
7
8 144 0.05 was considered as the statistically significant. Analyses were performed using R version 3.5.3
9
10 145 (R Foundation for Statistical Computing, Vienna, Austria).

11
12 146

147 **Patient and public involvement**

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

19
20 149

150 **Results**

151 There were 15,959 participants (10,023 males) included in this study. The average number of
152 health checkup for each participant was 2.62. Participants had a mean age of 37.38 years (SD:
153 13.27) and a mean SUA of 367.05 μ mol/L (SD: 97.97) at baseline, respectively. There were 1,227
154 (7.6%) participants that were obese at baseline. Significant differences between the obese and
155 non-obese groups were observed for SUA, age, gender, SBP, DBP, TC, TG, HDL-c, LDL-c, FPG,
156 BUN, and CR (p-value < 0.001) (**Table 1**). In total, the prevalence of obesity was approximately
157 14.2% for high SUA level. Obesity prevalence significantly increased with elevating SUA in the
158 subgroup analysis by gender and age group (p-value < 0.001). The prevalence was higher in males
159 than females. However, the prevalence had no obvious trend for by age groups (**Table 2**). The
160 prevalence of obesity significantly increased with the number of medical checkup years in the
161 group with high SUA and normal SUA levels (p<0.001 for trend) (**Figure 1**). Finally, 1078
162 participants developed obesity over the 9-year period.

163

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

1
2
3
4 168 greater among those with high level of SUA, males and younger participants. Likewise, with
5
6 169 longitudinal data on the repeated medical checkups in the multivariable GEE model (Model 2),
7
8 170 consistent risk factors for obesity were obtained. The estimates were observed as follows: [per-1
9
10 171 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
11
12 172 (95% CI: 1.32,1.60) for male, and OR =1.01 (1.01, 1.02) for age. In additional analysis by
13
14 173 categorical variables, we observed similar results with higher risk in male and elderly participants.

15
16 174

17
18 175 As showed in **Table 4**, similar results for GEE model analyses were observed in subgroup
19
20 176 analyses. Significant associations between SUA and risk of obesity were observed, where female
21
22 177 [per-SD OR=2.35 (2.16,2.55)] and young participants [per-SD OR=1.87 (1.80,1.94)] had an
23
24 178 elevated risk. We also did the analysis of baseline uric acid values vs obesity at the 9-year mark in
25
26 179 males and females, respectively where one eliminates baseline cases with hypertension, diabetes
27
28 180 or elevated BS, dyslipidemia, normal kidney function, baseline obesity. This result was consistent
29
30 181 with the subgroup analysis and well validate the data.

31
32
33 182

34
35 183 To calculate the discrimination ability of SUA among obese participants at different times of
36
37 184 medical checkup (1 to 8) or different years of medical checkup (2010 to 2018), ROC curves were
38
39 185 calculated. **SFigure 1** and **SFigure 2** summarizes the cut-off values and the area under receiver
40
41 186 operating curves (AUCs) of SUA in obesity participants stratified by gender. We found that the
42
43 187 overall cut-off values of SUA were 429.5 μ mol/L (range: 411.5-488.5 μ mol/L) in males
44
45 188 and 326.9 μ mol/L (range: 298.5-426.5 μ mol/L) in females when stratified by different times of
46
47 189 medical checkups. Similarly, we calculated the overall cut-off values for SUA, which were 429.5
48
49 190 μ mol/L (range: 366.7-431.5 μ mol/L) in males and 326.9 μ mol/L (range: 301.5-362.1 μ mol/L) in
50
51 191 females when stratified by different years of medical checkups.

52
53
54 192

55
56 193 **Discussion**

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

194 To the best of our knowledge, this is the first longitudinal study that estimated the relationship
195 between SUA and obesity over a long time period in China. The prevalence of obesity was
196 approximately 14.2% for high SUA level. Previous studies found that the prevalence of
197 hyperuricemia ranged from 2.5 to 25 % depending on the study population country ¹⁸. For instance,
198 the prevalence rates were reported to be 5 % in the Caucasus and 24.4 % in Thailand^{19, 20}. Overall,
199 we found high SUA level was associated with increased risk of obesity, within OR value of 1.85
200 (1.77, 1.91) in the GEE model for all participants, which was nearly consistent with prior studies ²¹,
201 ²². Currently, obesity and hyperuricemia, as well as their associated health complications (e.g.
202 metabolic syndrome) have emerged as a major public health concern as a result of the growing
203 prevalence, and the estimated economic burden⁷.

204

205 Several recent studies have investigated the mechanism of SUA on increasing the risk of obesity,
206 suggesting the influence of overproduction and poor renal excretion²³. Prior studies reported that
207 increased SUA level is closely related to excessive production of UA and the reduction of urinary
208 uric acid excretion and clearance ²⁴. This ultimately leads to increased risk of patients with
209 visceral fatty obesity²³. Visceral fat accumulation (VFA) results in a large influx of plasma free
210 fatty acids into the portal vein and liver. This stimulates the synthesis of triglycerides and
211 subsequently produced large amounts of UA through the activated UA synthesis pathway^{25, 26}.
212 Additionally, many researchers have reported a significant correlation between VFA and BMI²⁷,
213 ²⁸. Therefore, because of the close biological relationship between UA and BMI, it is of great
214 importance for preventive medicine to pay attention to the interaction between UA and BMI.

215

216 Conflicting results regarding gender and age differences for the association between SUA and
217 obesity have been reported^{10, 29}. Our study found significant differences in obesity participants with
218 elevated OR value among high SUA level, male, and elderly for all medical checkup participants.
219 A similar study reported a positive relationship between BMI and SUA levels among healthy
220 individuals in China³⁰. Nevertheless, in this study the subgroup analyses showed that significant

1
2
3
4 221 associated risk between SUA and obesity were observed higher in female and young participants.
5
6 222 This is consistent with a Thailand study that reported high SUA concentrations were associated
7
8 223 with greater risk of obesity in females³¹. However, study in Bangladesh and Japan reported that
9
10 224 elevated SUA predicted obesity higher in males and the elderly^{8, 29, 31}. Perhaps the associations of
11
12 225 SUA with obesity varies by populations. Moreover, in a 10-year follow-up study, BMI was
13
14 226 observed to significantly increase with higher SUA levels regardless of race and gender ³².
15
16 227 Therefore, greater attention should be provided to those vulnerable populations in clinical
17
18 228 guidelines.

19
20 229

21
22 230 An important observation was that association between SUA and risk of obesity in the LRM
23
24 231 [OR=1.84 (1.77,1.90)] for data at baseline was nearly consistent with the analyses in the GEE
25
26 232 model [OR= (1.85 (1.77,1.91)] for 9-year all participants. The risk of obesity within
27
28 233 hyperuricemia remained stable over the years. Therefore, short-term medical checkup results can
29
30 234 reflect the development of chronic diseases³³. Regarding the assessment of cut-off values from
31
32 235 ROC of SUA in obesity participants, the cut-off values of SUA were 429.5 μ mol/L in
33
34 236 males and 326.9 μ mol/L in females in stratified analysis by times or years of medical checkup. The
35
36 237 cut-off value was approximately consistent with the international standard for males³⁴. However, it
37
38 238 was underestimated for women in the group of obese participants. Perhaps the proportion of
39
40 239 females were fewer in this study. The cut-off values for SUA in the study may be useful for
41
42 240 distinguishing tests among obesity and non-obesity participants, which were significant for certain
43
44 241 risk value prediction and guidance³⁵.

45
46 242

47
48
49 243 To our knowledge, we must note several limitations in the present study. First, the underlying
50
51 244 mechanism by which SUA is increased in obese individuals remains not well understood. Second,
52
53 245 this study did not collect information on whether participants were prescribed medication to treat
54
55 246 hyperuricemia. Additionally, some medications used to treat hypertension may increase uric acid
56
57 247 levels. Third, there are numerous confounding factors that have not been considered, which can be

1
2
3
4 248 studied together with questionnaires in the future. Moreover, the younger screening population in
5
6 249 this study may underestimate the increased risk of uric acid among the elderly obese.
7

8
9 250

10
11 251 The present study has several strengths that must be noted. First, to our knowledge this is the first
12
13 252 large long-term medical checkup study to explore the relationship between SUA and obesity in
14
15 253 China. Second, the study analysis was based on the GEE model with high quality data by
16
17 254 controlling for confounding factors, which can increase the accuracy of the prediction. Third,
18
19 255 participants were representative of the general population with regard to clinical checkup and
20
21 256 obesity status, enhancing the generalizability of our findings. Moreover, results from this study
22
23 257 could inform prevention methods for obesity, especially in medically underserved areas where
24
25 258 medical service is insufficient.
26

27
28 259

29
30 260 This study filled current gaps in literature by analyzing the relationship between SUA and obesity
31
32 261 using medical checkup data. We observed that medical checkup data can be used to improve the
33
34 262 risk of obesity prediction accuracy. The medical checkup data used in this study can help provide
35
36 263 information that will facilitate intervention development and adoption at the individual level ³⁶.
37
38 264 The utility of medical checkup data can potentially reach beyond predictive power alone in the
39
40 265 near future.
41

42
43 266

44 45 267 **Conclusions**

46
47 268 In conclusion, our study observed significant associations between SUA and obesity in this 9-year
48
49 269 longitudinal study. We mainly found higher SUA level was associated with increased risk of
50
51 270 obesity. The prevalence of obesity was approximately 14.2% and significantly increased with the
52
53 271 number of medical checkup years in the group with high level of SUA. Additionally, the increased
54
55 272 risk of obesity was greater for high SUA level, male, and elderly participants. Subgroup analyses
56
57 273 revealed significant associations between SUA and obesity with higher risk for females and young
58
59
60

1
2
3
4 274 participants. Additionally, the cut-off for SUA on risk of obesity were approximately consistent
5
6 275 with the international standard. More evidence from well-designed studies are needed to confirm
7
8 276 our findings.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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.

Funding:

Research grants from the Science Foundation of Guangdong Second Provincial General Hospital (YQ2019-008).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Reference

1. Nagahama S, Kashino I, Hu H, Nanri A, Kurotani K, Kuwahara K *et al.* Haemoglobin A1c and hearing impairment: longitudinal analysis using a large occupational health check-up data of Japan. *BMJ open* 2018; **8**(9): e023220.
2. Kim YJ, Park H. Improving Prediction of High-Cost Health Care Users with Medical Check-Up Data. *Big data* 2019; **7**(3): 163-175.
3. Global Burden of Disease Study C. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**(9995): 743-800.
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9945): 766-81.
5. Liu R, Han C, Wu D, Xia X, Gu J, Guan H *et al.* Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *BioMed research international* 2015; **2015**: 762820.
6. Ishizaka N, Ishizaka Y, Toda A, Tani M, Koike K, Yamakado M *et al.* Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. *The Journal of rheumatology* 2010; **37**(2): 410-6.
7. Chen MY, Zhao CC, Li TT, Zhu Y, Yu TP, Bao YQ *et al.* Serum uric acid levels are associated with obesity but not cardio-cerebrovascular events in Chinese inpatients with type 2 diabetes. *Scientific reports* 2017; **7**: 40009.
8. Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X *et al.* Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. *European journal of epidemiology* 2013; **28**(8): 669-76.
9. Johnson RJ, Lanaspas MA, Gaucher EA. Uric acid: a danger signal from the RNA world that may have a role in the epidemic of obesity, metabolic syndrome, and cardiorenal disease: evolutionary considerations. *Seminars in nephrology* 2011; **31**(5): 394-9.
10. Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. 2018; **13**(11): e0206850.
11. Yang C, Yang S, Feng C, Zhang C, Xu W, Zhang L *et al.* Associations of hyperuricemia and obesity with remission of nonalcoholic fatty liver disease among Chinese men: A retrospective cohort study. *PloS one* 2018; **13**(2): e0192396.
12. Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic

- 1
2
3 syndrome in women and men. *Metabolism: clinical and experimental* 2008; **57**(6): 845-52.
4
5
6 13. You L, Liu A, Wuyun G, Wu H, Wang P. Prevalence of hyperuricemia and the relationship
7 between serum uric acid and metabolic syndrome in the Asian Mongolian area. *Journal of*
8 *atherosclerosis and thrombosis* 2014; **21**(4): 355-65.
9
10 14. WHO. Appropriate body-mass index for Asian populations and its implications for policy and
11 intervention strategies. *Lancet* 2004; **363**(9403): 157-63.
12
13 15. Li MF, Ren Y, Zhao CC, Zhang R, Li LX, Liu F *et al.* Prevalence and clinical characteristics of
14 lower limb atherosclerotic lesions in newly diagnosed patients with ketosis-onset diabetes: a
15 cross-sectional study. *Diabetology & metabolic syndrome* 2014; **6**: 71.
16
17 16. Buzkova P, Brown ER, John-Stewart GC. Longitudinal data analysis for generalized linear
18 models under participant-driven informative follow-up: an application in maternal health
19 epidemiology. *American journal of epidemiology* 2010; **171**(2): 189-97.
20
21 17. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off
22 value: the case of tests with continuous results. *Biochemia medica* 2016; **26**(3): 297-307.
23
24 18. Remedios C, Shah M, Bhasker AG, Lakdawala M. Hyperuricemia: a reality in the Indian obese.
25 *Obesity surgery* 2012; **22**(6): 945-8.
26
27 19. Uaratanawong S, Suraamornkul S, Angkeaw S, Uaratanawong R. Prevalence of hyperuricemia
28 in Bangkok population. *Clinical rheumatology* 2011; **30**(7): 887-93.
29
30 20. Ford DK, Demos AM. Serum Uric Acid Levels of Healthy Caucasian, Chinese and Haida Indian
31 Males in British Columbia. *Canadian Medical Association journal* 1964; **90**: 1295-7.
32
33 21. Kuwabara M, Kuwabara R, Hisatome I, Niwa K, Roncal-Jimenez CA, Bjornstad P *et*
34 *al.* "Metabolically Healthy" Obesity and Hyperuricemia Increase Risk for Hypertension and
35 Diabetes: 5-year Japanese Cohort Study. *Obesity* 2017; **25**(11): 1997-2008.
36
37 22. Zhang N, Chang Y, Guo X, Chen Y, Ye N, Sun Y. A Body Shape Index and Body Roundness
38 Index: Two new body indices for detecting association between obesity and hyperuricemia in
39 rural area of China. *European journal of internal medicine* 2016; **29**: 32-6.
40
41 23. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T *et al.* Effect of
42 visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity
43 is linked more closely to overproduction of uric acid than subcutaneous fat obesity.
44 *Metabolism: clinical and experimental* 1998; **47**(8): 929-33.
45
46 24. Han T, Meng X, Shan R, Zi T, Li Y, Ma H *et al.* Temporal relationship between hyperuricemia
47 and obesity, and its association with future risk of type 2 diabetes. *International journal of*
48 *obesity (2005)* 2018; **42**(7): 1336-1344.
49
50 25. Fabregat I, Revilla E, Machado A. Short-term control of the pentose phosphate cycle by
51 insulin could be modulated by the NADPH/NADP ratio in rat adipocytes and hepatocytes.
52 *Biochemical and biophysical research communications* 1987; **146**(2): 920-5.
53
54
55
56
57
58
59
60

- 1
2
3 26. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism: clinical and experimental* 1981; **30**(6): 616-34.
- 4
5
6 27. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circulation journal : official journal of the Japanese Circulation Society* 2002; **66**(11): 987-92.
- 7
8
9
10
11 28. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S *et al.* Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes research and clinical practice* 2009; **83**(1): 100-5.
- 12
13
14
15
16 29. Tanaka K, Ogata S, Tanaka H, Omura K, Honda C, Hayakawa K. The relationship between body mass index and uric acid: a study on Japanese adult twins. *Environmental health and preventive medicine* 2015; **20**(5): 347-53.
- 17
18
19
20 30. Wang H, Wang L, Xie R, Dai W, Gao C, Shen P *et al.* Association of Serum Uric Acid with Body Mass Index: A Cross-Sectional Study from Jiangsu Province, China. *Iranian journal of public health* 2014; **43**(11): 1503-9.
- 21
22
23
24
25 31. Jaipakdee J, Jiamjarasrangsri W, Lohsoonthorn V, Lertmaharit S. Prevalence of metabolic syndrome and its association with serum uric acid levels in Bangkok Thailand. *The Southeast Asian journal of tropical medicine and public health* 2013; **44**(3): 512-22.
- 26
27
28
29
30 32. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *European journal of epidemiology* 2007; **22**(7): 439-45.
- 31
32
33
34 33. Nohara Y, Kai E. Health checkup and telemedical intervention program for preventive medicine in developing countries: verification study. 2015; **17**(1): e2.
- 35
36
37 34. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Current opinion in rheumatology* 2014; **26**(2): 186-91.
- 38
39
40
41 35. Mongioi LM, Condorelli RA, Barbagallo F, Cannarella R, La Vignera S, Calogero AE. Accuracy of the Low-Dose ACTH Stimulation Test for Adrenal Insufficiency Diagnosis: A Re-Assessment of the Cut-Off Value. *Journal of clinical medicine* 2019; **8**(6).
- 42
43
44
45 36. Taninaga J, Nishiyama Y. Prediction of future gastric cancer risk using a machine learning algorithm and comprehensive medical check-up data: A case-control study. 2019; **9**(1): 12384.
- 46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 **Tables and Figure legends:**

5 **Table 1.** Baseline characteristics and comparison between obesity and non-obesity
6 participants.
7
8

9
10
11 **Table 2.** The prevalence of obesity by gender, age of checkup stratified by baseline SUA.
12

13
14
15 **Table3.** Relationship between risk factors and risk of obesity in the models.
16

17
18 **Table 4.** Relationship between risk factors and risk of obesity in the models stratified by gender
19 and age group.
20

21
22
23
24 **Figure 1.** Location of Guangdong Second Provincial General Hospital (Guangzhou,
25 Guangdong, China) and the prevalence of obesity by different years stratified by baseline
26 SUA.
27
28

29
30
31 **Figure 2.** Flow diagram showing selection process of participants in our study.
32

33
34
35
36
37
38 **Supplemental data:**

39
40
41 **Supplementary Figure1.** The ROC curves showing the relationship between SUA and risk of
42 obesity stratified by gender and different times of medical checkups.
43

44
45
46 **Supplementary Figure2.** The ROC curves showing the relationship between SUA and risk of
47 obesity stratified by gender and different years of medical checkups (from 2010 to 2018).
48
49

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

Characteristics	All patients	Obesity ^a	Non-obesity	<i>p</i> -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.

^aObesity was defined as body mass index (BMI) ≥ 28.0 kg/m².

^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

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.

^aObesity 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	
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

^dModel 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).

^eHigh 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			
	Male		Female	
Gender	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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)	
	<i>OR^a (95%CI^b)</i>	<i>p-value</i>	<i>OR^a (95%CI^b)</i>	<i>p-value</i>
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

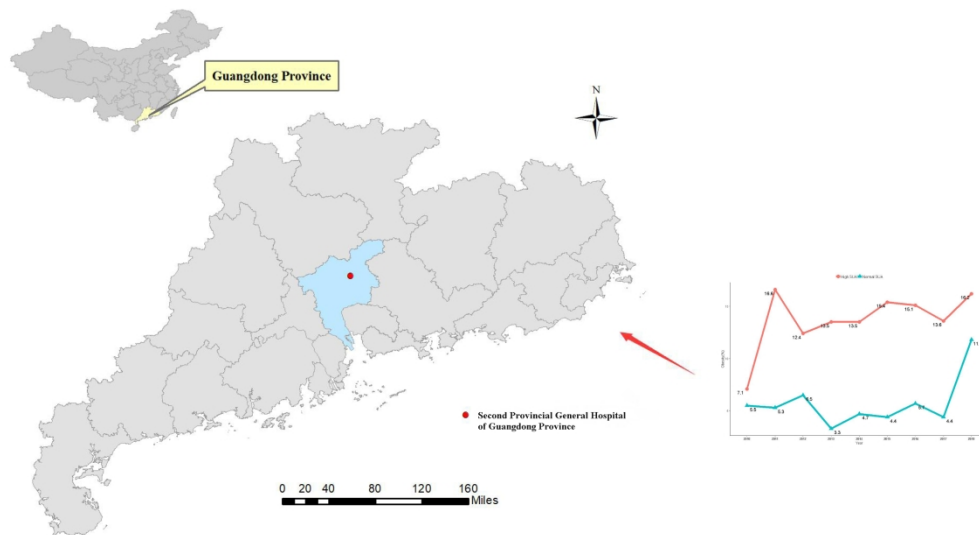
Note: ^aOR: odds ratio; ^bCI: confidence interval.

^cModel 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).

^eHigh 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.

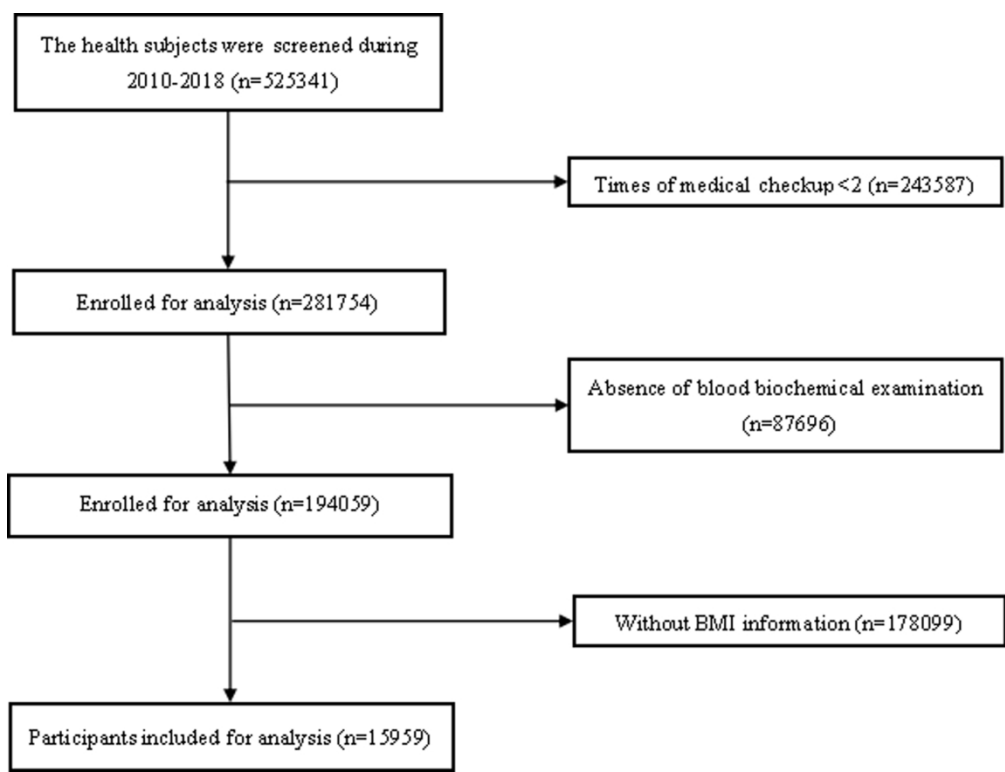
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

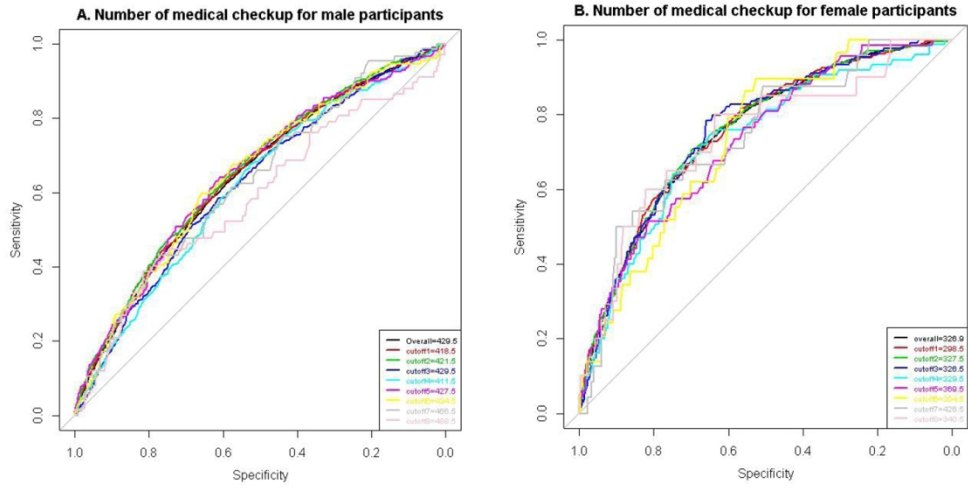


240x140mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

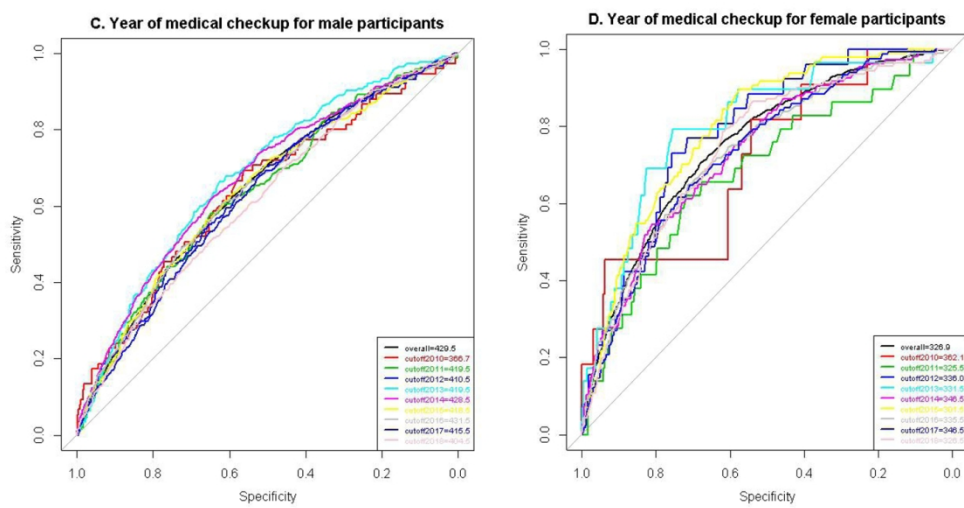


155x117mm (300 x 300 DPI)



127x63mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



127x64mm (300 x 300 DPI)

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	8-9
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	8-9

Continued on next page

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15 *	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	9-10
		<i>Cross-sectional study</i> —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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

*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.

For peer review only