

1 **Abstract**

2 **Objectives:** To evaluate the association between hypouricemia and cardiometabolic  
3 diseases, such as hypertension, dyslipidemia, and reduced kidney function, and to  
4 explore the sex-specific optimal range for serum uric acid (sUA) associated with the  
5 lowest risk for these diseases.

6 **Methods:** In this cross-sectional study, we identified individuals with sUA data  
7 between April 2018 and March 2019 and recorded the frequency of cardiometabolic  
8 comorbidities according to sUA. Univariable and multivariable logistic regression  
9 analyses were performed for the overall population, and after classifying by sex to  
10 assess the association between sUA and cardiometabolic comorbidities.

11 **Results:** Among 796,508 individuals, a J-shaped association was observed between  
12 the sUA level and cardiometabolic diseases in the overall population. The adjusted  
13 odds ratios (95% confidence interval) for hypertension, dyslipidemia, and reduced  
14 renal function in individuals with sUA  $\leq 1.0$  mg/dL compared with those with sUA  
15 ranging between 2.1–3.0 mg/dL were 1.38 (1.13–1.69), 1.52 (1.30–1.78), and 2.17  
16 (1.47–3.20), respectively. A J-shaped association between sUA and hypertension  
17 was observed only in women. The optimal range of sUA associated with the lowest  
18 risk for hypertension was assumed to be  $<6$  mg/dL in men and 1–4 mg/dL in women.  
19 A J-shaped association between the sUA and dyslipidemia and reduced renal  
20 function was observed in both men and women. The optimal range of sUA for  
21 dyslipidemia and reduced renal function was approximately 2–5 mg/dL in men and  
22 1–4 mg/dL in women.

23 **Conclusions:** Excess and extremely low uric acid levels may be related to an  
24 increased cardiometabolic risk.

25

26 **Key Indexing Terms:** Hypouricemia, Hyperuricemia, Uric Acid, Urate, Epidemiology

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29

## 30 **Introduction**

31 Previous epidemiological studies have shown that hyperuricemia is a risk factor for  
32 cardiovascular diseases as well as all-cause and cardiovascular-related mortality.<sup>1,2</sup>  
33 Furthermore, a J-shaped or U-shaped association has been reported between the  
34 serum uric acid (sUA) levels and cardiovascular disease and mortality. Both high and  
35 low levels of sUA are possibly associated with an increased cardiovascular risk.<sup>3-5</sup>  
36 For example, a previous observational study showed that sUA <4.5 mg/dL in men  
37 and <3.2 mg/dL in women with hypertension was associated with increased  
38 cardiovascular risk.<sup>3</sup> However, the association between hypouricemia and  
39 cardiovascular risk remains unclear.<sup>1,6,7</sup> Moreover, a recent study assessed a J-  
40 shaped association between the sUA levels and cardiometabolic diseases.<sup>8-10</sup>  
41 Cardiometabolic diseases includes abnormal test values associated with circulatory  
42 and metabolic diseases, such as hypertension and reduced kidney function.<sup>8,11</sup>  
43 However, the lowest sUA level categories were  $\leq 2.0$  mg/dL in those studies,<sup>8-10</sup> and  
44 no study has assessed even lower sUA levels ( $\leq 1.0$  mg/dL).

45 We previously assessed large-scale medical check-up and health insurance  
46 claims data and reported that individuals with extreme hypouricemia (sUA level  $\leq 1.0$   
47 mg/dL) had a higher prevalence of cardiometabolic diseases compared to those with  
48 less severe hypouricemia ( $1.0 \text{ mg/dL} < \text{sUA} \leq 2.0 \text{ mg/dL}$ ).<sup>12</sup> Furthermore, the  
49 characteristics of individuals with hypouricemia differ between the sexes.<sup>12</sup> As  
50 individuals with hypouricemia with more extreme sUA levels are not frequently  
51 observed, an epidemiological study using a large enough sample size to accurately  
52 assess the influence of low sUA levels on cardiometabolic risk is necessary.

53 Therefore, we aimed to evaluate the correlation between hypouricemia and  
54 cardiometabolic diseases, such as hypertension, dyslipidemia, and reduced kidney

55 function, and to explore the optimal range of sUA levels separately for men and women  
56 in the general population.

57

## 58 **Materials and Methods**

### 59 ***Study Design and Setting***

60 This cross-sectional study utilized the JMDC Claims Database, including records of  
61 medical check-ups and health insurance claims data from April 2018 to March 2019.  
62 JMDC Inc. (Tokyo, Japan) collects reimbursement information from multiple health  
63 insurance societies for company employees and their family members aged <75  
64 years. As of June 2020, approximately 9.8 million insured individuals were included  
65 in this database.<sup>13</sup> Data included information from medical check-ups, diagnostic  
66 codes using the International Classification of Diseases 10<sup>th</sup> revision (ICD-10) codes,  
67 and drug prescriptions using Anatomical Therapeutic Chemical (ATC) codes for each  
68 person. Health insurance companies require annual medical check-ups to ascertain  
69 the overall health of insured individuals.<sup>13</sup> An individual's medical information can be  
70 tracked, even if the individual visited multiple medical facilities, provided that the  
71 facility belongs to the respective health insurance network. The database is widely  
72 used for epidemiological studies in Japan.<sup>12, 14–18</sup> This study was approved by the  
73 Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine  
74 (approval number R2383). The need to obtain informed consent from individual  
75 patient was waived since the data were anonymized.

76

### 77 ***Participants***

78 We identified individuals who had sUA readings taken at least once during medical  
79 check-ups between April 1, 2018, and March 31, 2019, and were enrolled in the

80 JMDC claims database at least 6 months prior to the first medical check-up. We  
81 excluded individuals whose sUA levels exceeded 20.0 mg/dL, which is regarded as  
82 clinically inappropriate because the maximum value of sUA in clinical settings is  
83 approximately 17 mg/dL,<sup>19,20</sup> and sUA levels >20.0 mg/dL are extremely rare. We  
84 also excluded individuals with missing data that were required for the analyses. All  
85 individuals who met the eligibility criteria were included to eliminate selection bias.

86

### 87 **Definitions**

88 We identified the disease history 6 months before the first check-up using the ICD-10  
89 codes. The history of diseases of interest to the study were included, such as  
90 diagnosed renal dysfunction, urinary stones, cardiovascular disease,  
91 cerebrovascular disease, and neurological diseases including Parkinson's and  
92 Alzheimer's disease, which have been linked to hypouricemia.<sup>7,12</sup> We defined a  
93 prescribed drug as concomitant medication if its prescription period included the date  
94 of the first check-up date, using the ATC codes. The definition is summarized in  
95 Table S1, Supplemental Digital Content.

96 We identified cardiometabolic comorbidities by using data from concomitant  
97 medications and medical check-ups conducted on the same day that the sUA levels  
98 were quantified. Hypertension was defined as prescription of anti-hypertensive  
99 drugs, a systolic blood pressure (BP)  $\geq 140$  mmHg, and/or a diastolic BP  $\geq 90$   
100 mmHg.<sup>21</sup> Dyslipidemia was defined as prescription of anti-lipidemic drugs, low-  
101 density lipoprotein cholesterol level  $\geq 140$  mg/dl, high-density lipoprotein cholesterol  
102 level  $< 40$  mg/dL, and/or a triglyceride level  $\geq 150$  mg/dL.<sup>22</sup> Reduced kidney function  
103 was defined as an estimated glomerular filtration rate (eGFR)  $< 60$  mL/min/1.73m<sup>2</sup>,  
104 which was calculated using the following formula:

105  $eGFR \text{ (ml/min/1.73m}^2\text{)} = 194 \times Cr^{-1.094} \times age^{-0.287} (\times 0.739 \text{ for women})$  <sup>23</sup>

106 Diabetes mellitus was defined as prescription of anti-diabetic drugs and/or a  
107 hemoglobin A1c (HbA1c) level  $\geq 6.5\%$ .<sup>24</sup>

108

### 109 **Statistical Methods**

110 The data were analyzed overall and separately based on sex. The results are  
111 reported as means and standard deviations (SD) for continuous variables, and as  
112 numbers and percentages for categorical variables. We divided the participants into  
113 nine categories according to their sUA levels:  $\leq 1.0$ , 1.1–2.0, 2.1–3.0, 3.1–4.0, 4.1–  
114 5.0, 5.1–6.0, 6.1–7.0, 7.1–8.0, and  $\geq 8.1$  mg/dL, so that we could evaluate the  
115 cardiometabolic risk per 1 mg/dL of sUA. If the participant's sUA was examined more  
116 than once, the results from the first examination were used for the analysis to avoid  
117 double counting. We described participant characteristics and cardiometabolic  
118 comorbidities according to the nine sUA categories.

119 Univariable and multivariable logistic regression analyses were performed to  
120 estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) (with sUA  
121 levels of 2.1–3.0 mg/dL as a reference category) to assess the association between  
122 sUA and the following cardiometabolic comorbidities: 1) hypertension, 2)  
123 dyslipidemia, and 3) reduced renal function. We did not investigate the association  
124 between hypouricemia and diabetes mellitus, since diabetes mellitus is established  
125 as a possible cause of hypouricemia.<sup>7</sup> In Model 1 for hypertension, we adjusted for  
126 age, sex, body mass index (BMI), waist circumference, smoking, drinking habit,  
127 eGFR, diabetes mellitus, dyslipidemia, history of ischemic heart disease, heart  
128 failure, and cerebrovascular disease. In Model 2 for dyslipidemia, we adjusted for  
129 age, sex, BMI, waist circumference, smoking, drinking habits, diabetes mellitus,

130 hypertension, and history of ischemic heart disease, heart failure, and  
131 cerebrovascular disease. In Model 3 for reduced renal function, we adjusted for age,  
132 sex, BMI, waist circumference, smoking, drinking habits, diabetes mellitus,  
133 hypertension, dyslipidemia, history of renal dysfunction, and heart failure.

134 Subgroup analysis was conducted in participants who were not prescribed  
135 drugs that affect the serum uric acid levels. We excluded those undergoing urate-  
136 lowering therapy (ULT) as well as those receiving losartan, an angiotensin II receptor  
137 blocker, and fenofibrate, an antilipotropic drug, which have been reported to  
138 decrease the serum uric acid levels.<sup>7</sup> A subgroup analysis stratified by diabetes  
139 mellitus was conducted, as diabetes mellitus is linked to both hypouricemia and  
140 hyperuricemia.<sup>7,25</sup> Univariable and multivariable logistic regression analyses were  
141 performed using Models 1, 2, and 3.

142 All statistical analyses were conducted using SAS version 9.4 (SAS Institute  
143 Inc., Cary, NC, USA).

144

145

## 146 **Results**

### 147 ***Study Population***

148 We identified 796,508 individuals who met the inclusion criteria and not the exclusion  
149 criteria for inclusion in our analysis (Figure 1).

150

### 151 ***Participant Characteristics Classified by sUA Categories***

152 The participant characteristics classified by sUA categories for the participants  
153 included in the analysis are summarized in Table 1. The mean age (SD) of the  
154 participants was 44.7 (10.4) years, of which 60.8% (n=484,103) were men, and the

155 mean sUA (SD) level of the overall population was 5.5 (1.4) mg/dL. In this  
156 population, the sex distributions varied significantly among the sUA categories. Men  
157 accounted for 11.5% (n=2,277) of the participants with sUA levels of 2.1–3.0 mg/dL,  
158 and 97.5% (n=31,073) of those had sUA levels  $\geq$ 8.1 mg/dL (Table 1, Figure S1 –  
159 Supplemental Digital Content).

160 The frequency of renal dysfunction, urinary stones, ischemic heart disease,  
161 and heart failure were least frequent in participants with sUA levels of 2.1–4.0 mg/dL  
162 as compared to other sUA levels. In contrast, neurological diseases, including  
163 Parkinson’s disease, were most frequent in the participants with sUA levels in the  
164 range of 1.1–2.0 mg/dL (Table 1) as opposed to other sUA levels. Overall,  
165 neurological diseases mainly consisted of sleep disorders (49.6%), other and  
166 unspecified polyneuropathies (12.6%), and migraines (7.5%), while other diseases  
167 constituted <5% of cases.

168

### 169 ***Participant Characteristics Classified Based on Sex***

170 The participant characteristics for the different sUA level categories for men and  
171 women are shown in Tables S2 and S3 (Supplemental Digital Content), respectively.

172 Among men, the mean age (SD) of participants was 44.7 (10.5) years and the  
173 mean sUA (SD) level was 6.2 (1.2) mg/dL. Renal dysfunction, ischemic heart  
174 disease, and neurological diseases, including Parkinson’s disease, were the most  
175 frequent pathologies in participants with sUA levels of 1.1–2.0 mg/dL as compared to  
176 other sUA levels. Heart failure and cerebrovascular disease were most frequently  
177 reported in participants with sUA levels of 2.1–3.0 mg/dL as compared to other sUA  
178 levels (Table S2, Supplemental Digital Content).



179           Among women, the mean age (SD) of participants was 44.6 (10.2) years and  
180 the mean sUA (SD) level was 4.5 (1.0) mg/dL. Participants with low levels of sUA  
181 had a low frequency of most diseases (Table S3, Supplemental Digital Content).

182

### 183 ***Frequency of Cardiometabolic Comorbidities for Each sUA Category***

184 The frequency of cardiometabolic comorbidities for each sUA category is presented  
185 in Table S4 (Supplemental Digital Content). The frequency of cardiometabolic  
186 comorbidities was lowest in participants with sUA levels of 2.1–3.0 mg/dL in the  
187 overall population. Therefore, this category was selected as the reference category  
188 for the univariable and multivariable logistic regression analyses to ascertain the  
189 association of sUA and cardiometabolic comorbidities. Among men, hypertension,  
190 dyslipidemia, and reduced kidney function were the least frequent comorbidities in  
191 those with sUA levels of 4.1–5.0, 2.1–3.0, and 3.1–4.0 mg/dL, respectively. Among  
192 women, hypertension and reduced kidney function were the least frequent  
193 comorbidity in those with sUA levels of 1.1–2.0 mg/dL, and dyslipidemia was the  
194 least frequent comorbidity in those with sUA levels of 2.1–3.0 mg/dL.

195

### 196 ***Association Between Serum Uric Acid and Cardiometabolic Comorbidities***

197 The association between the sUA levels and hypertension is shown in Figure 2. Crude  
198 and adjusted ORs and their 95% CIs used in ascertaining the association between  
199 sUA and hypertension are shown in Table S5 (Supplemental Digital Content). In the  
200 overall population, a J-shaped association was observed between sUA and  
201 hypertension. Participants with lower levels of hypouricemia (sUA  $\leq$ 1.0 mg/dL) had an  
202 adjusted OR (95% CI) of 1.38 (1.13–1.69) when compared with those in the reference  
203 category with sUA levels of 2.1–3.0 mg/dL, while those with hyperuricemia (sUA levels

204 of 7.1–8.0 mg/dL and  $\geq 8.1$  mg/dL) had adjusted ORs (95% CIs) of 2.07 (1.96–2.20)  
205 and 2.59 (2.44–2.75), respectively. A J-shaped association between sUA and  
206 hypertension was observed in women only. The optimal range of sUA that was  
207 associated with the lowest risk for hypertension was assumed to be  $< 6$  mg/dL in men  
208 and 1–4 mg/dL in women. This was attributed to the fact that a significant increase in  
209 the adjusted OR was observed in the category of participants with sUA levels  $\geq 6.1$   
210 mg/dL among men and those with sUA levels  $\leq 1.0$  mg/dL and  $\geq 4.1$  mg/dL among  
211 women.

212 The association between sUA and dyslipidemia is shown in Figure 3. Crude and  
213 adjusted ORs and their 95% CIs for the association between sUA and dyslipidemia  
214 are summarized in Table S6 (Supplemental Digital Content). In the overall population,  
215 a J-shaped association between sUA and dyslipidemia was observed: participants with  
216 sUA levels  $\leq 1.0$  mg/dL had an adjusted OR (95% CI) of 1.52 (1.30–1.78) compared  
217 with those in the reference category. Furthermore, participants with hyperuricemia  
218 (sUA levels of 7.1–8.0 mg/dL and  $\geq 8.1$  mg/dL) had adjusted ORs (95% CIs) of 3.27  
219 (3.14–3.41) and 4.68 (4.47–4.90), respectively. In both men and women, a J-shaped  
220 association between sUA and dyslipidemia was also observed. The optimal range of  
221 sUA for dyslipidemia was assumed to be approximately 2–5 mg/dL in men and 1–4  
222 mg/dL in women.

223 The association between the sUA levels and reduced renal function is  
224 presented in Figure 4. The crude and adjusted ORs and their 95% CIs for the  
225 association between sUA and reduced renal function are shown in Table S7  
226 (Supplemental Digital Content). In the overall population, a J-shaped association  
227 between sUA and reduced renal function was observed: participants with extreme  
228 (sUA level  $\leq 1.0$  mg/dL) and those with less serious (1.1–2.0 mg/dL) levels of

229 hypouricemia had adjusted ORs (95% CIs) of 2.17 (1.47–3.20) and 1.70 (1.10–2.62),  
230 respectively, when compared with the sUA levels of the participants in the reference  
231 category; participants with hyperuricemia (sUA levels of 7.1–8.0 mg/dL and  $\geq$ 8.1  
232 mg/dL) had adjusted ORs (95% CIs) of 9.70 (8.65–10.88) and 17.82 (15.86–20.03),  
233 respectively. A J-shaped association between sUA and reduced renal function was  
234 also observed in both men and women. The optimal range of sUA levels for reduced  
235 renal function was approximately 2–5 mg/dL in men and 1–4 mg/dL in women.

236

### 237 ***Subgroup Analysis***

238 The adjusted ORs and their 95% CIs for the associations between sUA and  
239 cardiometabolic comorbidities in the subgroup of participants without drugs that  
240 decrease the sUA levels are shown in Table S8 (Supplemental Digital Content). We  
241 identified 762,371 individuals who were not prescribed drugs that decrease the sUA  
242 levels. In this subgroup, the results were similar to the findings of the analysis of the  
243 overall population. A J-shaped association between sUA and cardiometabolic  
244 comorbidities was observed.

245 The adjusted ORs and their 95% CIs for the association between sUA and  
246 cardiometabolic comorbidities in the subgroup of participants without diabetes  
247 mellitus are summarized in Table S9 (Supplemental Digital Content). We conducted  
248 the analysis with 754,673 individuals who did not have diabetes mellitus. The results  
249 in this subgroup were also similar to those in the overall population.

250 The adjusted ORs and their 95% CIs for the association between sUA and  
251 cardiometabolic comorbidities in the subgroup of patients with diabetes mellitus are  
252 shown in Table S10 (Supplemental Digital Content). We conducted the analysis with  
253 41,835 patients who had diabetes mellitus. The adjusted ORs in patients with lower

254 and higher levels of hypouricemia were not significantly high compared to those in  
255 the reference category. A J-shaped association between the sUA and  
256 cardiometabolic comorbidities was not observed, unlike the results from the overall  
257 population.

258

259

## 260 **Discussion**

261 This study investigated the association between hypouricemia and cardiometabolic  
262 diseases, such as hypertension, dyslipidemia, and reduced kidney function. We also  
263 explored the optimal range of sUA levels for each sex that was associated with the  
264 lowest risk for cardiometabolic diseases. Our approach utilized large-scale medical  
265 check-up and health insurance claims data. We consistently observed a J-shaped  
266 association between sUA and cardiometabolic diseases in the overall population.  
267 The adjusted ORs for hypertension, dyslipidemia, and reduced renal function in  
268 participants with sUA levels  $\leq 1.0$  mg/dL when compared with those with sUA levels  
269 of 2.1–3.0 mg/dL were 1.38, 1.52, and 2.17, respectively, suggesting that extremely  
270 low uric acid levels are related to increased cardiometabolic risks.

271 Our results suggested that both excess and extremely low uric acid may be  
272 associated with increased cardiovascular risk. One of the possible mechanisms for  
273 the increased risk of cardiometabolic diseases is that extremely low uric acid causes  
274 an increase in oxidative stress and contributes to vascular endothelial dysfunction  
275 because uric acid is a powerful antioxidant.<sup>26–28</sup> In a previous study, participants who  
276 had sUA levels  $\leq 0.8$  mg/dL had mutations in both the URAT1/SLC22A12 alleles and  
277 often had endothelial dysfunction.<sup>29</sup>

278 We also investigated the sex-based associations of hypouricemia and the risk  
279 of cardiometabolic disease, and explored sex-specific optimal ranges for sUA levels  
280 associated with the lowest risk for these diseases. A J-shaped association between  
281 sUA and hypertension was observed in women only. The optimal range of sUA levels  
282 associated with a minimized risk of hypertension was assumed to be <6 mg/dL in men  
283 and 1–4 mg/dL in women. Another longitudinal observational study reported that “the  
284 optimal serum urate range associated with the reduced development of  
285 cardiometabolic diseases could be <5 mg/dL for men and 2–4 mg/dL for women in a  
286 generally healthy population,” which is in agreement with our observations.<sup>8</sup>  
287 Meanwhile, a J-shaped association between sUA and dyslipidemia and reduced renal  
288 function was observed in both men and women in our study. According to a previous  
289 cross-sectional population-based study, hypouricemia and reduced renal function  
290 were related only in men,<sup>10</sup> which differs from our findings. In that study, the lowest  
291 sUA level category was  $\leq 2.0$  mg/dL and the reference category had a sUA  
292 concentration of 4.1–5.0 mg/dL. These are possible reasons for why the elevated risk  
293 of sUA levels  $\leq 1.0$  mg/dL were not detected in women.

294 Our results suggest that the optimal range for sUA associated with the lowest  
295 risk of cardiometabolic disease appear to differ between the sexes. In men, sUA levels  
296  $\leq 2.0$  mg/dL were associated with dyslipidemia and reduced renal function. Conversely,  
297 in women, sUA levels  $\leq 1.0$  mg/dL were associated with an increased risk for these  
298 conditions, but not in participants with sUA levels of 1.1–2.0 mg/dL. It is possible that  
299 some women with sUA levels  $\leq 2.0$  mg/dL may have had female hormone-associated  
300 transient hypouricemia, while participants with extremely low sUA levels of 1.0 mg/dL  
301 may have had persistent hypouricemia due to a genetic mutation in the genes for urate  
302 transporter variants.<sup>30</sup>

303           The results from our subgroup analysis in participants who did not receive drugs  
304 that decrease the sUA levels and in participants without diabetes mellitus are also in  
305 agreement with the main results. In the patients with diabetes mellitus, a significant  
306 increase in the adjusted ORs was not observed in the low uric acid categories, but the  
307 CIs were wide because of the small sample size.

308           The strengths of this study include the utilization of sUA data from  
309 approximately 800,000 individuals from a large-scale real-world dataset. As we used  
310 data from employer-sponsored medical check-ups, we were able to obtain the sUA  
311 data from the general population. An adequate sample size made it possible to  
312 evaluate the category of individuals with sUA levels  $\leq 1.0$  mg/dL and to obtain new sex-  
313 specific findings regarding extremely low sUA levels.

314           However, this study has some limitations. First, as the JMDC database  
315 contains data from health insurance societies for company employees, data from  
316 individuals aged  $\geq 65$  years are limited, and data from those aged  $\geq 75$  years are  
317 absent. Second, although adjustments for confounders were performed, we cannot  
318 rule out the possibility of unknown or unmeasured confounding factors. Third, this  
319 was a cross-sectional study. Therefore, it was not possible to estimate a causal  
320 relationship between the sUA levels and cardiometabolic diseases. Intervention  
321 studies are needed to further elucidate whether ULT is useful in preventing the  
322 development of cardiometabolic diseases.

323           In conclusion, our study demonstrated a J-shaped association between sUA  
324 and cardiometabolic diseases, such as hypertension, dyslipidemia, and reduced  
325 renal function in the overall population, and suggests that both excess uric acid and  
326 extremely low uric acid levels may be related to elevated cardiometabolic risks.

327 These results suggest that routine checks for sUA levels may be useful in screening  
328 for cardiometabolic diseases in clinical settings.

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447 Table S10 Adjusted odds ratios and 95% confidence intervals for the association  
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449 the subgroup of patients with diabetes mellitus.

450

451 **Supplemental Figure**

452 Figure S1 Sex distribution of the overall population according to serum uric acid  
453 categories.

454

455

456 **Figure Legends**

457 Figure 1 Participant dispositions.

458

459 Figure 2 Forest plot showing adjusted odds ratios and 95% confidence intervals to  
460 establish the association between the serum uric acid levels and hypertension. (A)  
461 Overall population, (B) only men, and (C) only women.

462

463 Figure 3 Forest plot showing adjusted odds ratios and 95% confidence intervals to  
464 establish the association between the serum uric acid levels and dyslipidemia. (A)  
465 Overall population, (B) only men, and (C) only women.

466

467 Figure 4 Forest plot showing adjusted odds ratios and 95% confidence intervals to  
468 assess the association between the serum uric acid levels and reduced renal  
469 function. (A) Overall population, (B) only men, and (C) only women.

470

**Table 1** Participant characteristics classified by the serum uric acid categories of the population under analysis

	Serum uric acid category, mg/dL									
	≤1.0	1.1–2.0	2.1–3.0	3.1–4.0	4.1–5.0	5.1–6.0	6.1–7.0	7.1–8.0	8.1≤	Overall
	n=803	n=901	n=19,827	n=107,827	n=187,025	n=203,711	n=164,504	n=80,023	n=31,887	n=796,508
<b>Age, years,</b>	44.8	42.6	42.9	43.4	44.8	45.2	45.0	44.8	44.0	44.7
<b>mean (SD)</b>	(10.8)	(9.0)	(9.4)	(9.9)	(10.5)	(10.8)	(10.6)	(10.2)	(9.8)	(10.4)
<b>Sex, n (%)</b>										
<b>Male</b>	472 (58.8%)	126 (14.0%)	2,277 (11.5%)	17,415 (16.2%)	62,878 (33.6%)	145,137 (71.3%)	148,237 (90.1%)	76,488 (95.6%)	31,073 (97.5%)	484,103 (60.8%)
<b>Female</b>	331 (41.2%)	775 (86.0%)	17,550 (88.5%)	90,412 (83.9%)	124,147 (66.4%)	58,574 (28.8%)	16,267 (9.9%)	3,535 (4.4%)	814 (2.6%)	312,405 (39.2%)
<b>BMI, kg/m<sup>2</sup>,</b>	23.1	20.9	20.7	21.1	22.0	23.2	24.2	25.1	26.0	23.1
<b>mean (SD)</b>	(3.7)	(3.4)	(2.9)	(3.1)	(3.4)	(3.6)	(3.7)	(3.8)	(4.2)	(3.8)
<b>Waist circumference, cm, mean (SD)</b>	81.6 (10.2)	75.1 (9.3)	74.7 (8.2)	75.8 (8.7)	78.5 (9.4)	82.1 (9.5)	85.0 (9.6)	87.4 (9.8)	89.9 (10.4)	81.6 (10.2)
<b>Smoking, n (%)</b>	187 (23.3%)	111 (12.3%)	2,309 (11.7%)	13,824 (12.8%)	33,459 (17.9%)	56,601 (27.8%)	52,462 (31.9%)	26,748 (33.4%)	11,567 (36.3%)	197,268 (24.8%)
<b>Drinking habits, n (%)</b>	455 (56.7%)	339 (37.6%)	7,801 (39.4%)	46,507 (43.1%)	93,132 (49.8%)	122,489 (60.1%)	112,038 (68.1%)	57,954 (72.4%)	23,671 (74.2%)	464,386 (58.3%)
<b>Serum uric acid, mg/dL, mean (SD)</b>	0.7 (0.2)	1.8 (0.2)	2.7 (0.2)	3.6 (0.3)	4.6 (0.3)	5.6 (0.3)	6.5 (0.3)	7.5 (0.3)	8.7 (0.7)	5.5 (1.4)
<b>eGFR, mL/min/1.73m<sup>2</sup>, mean (SD)</b>	82.0 (14.2)	91.5 (22.0)	88.4 (16.8)	85.2 (15.4)	81.6 (14.9)	79.7 (14.5)	77.7 (14.2)	75.6 (14.2)	73.3 (14.9)	80.0 (15.1)
<b>History of disease, n (%)</b>										
<b>Renal dysfunction</b>	13 (1.6%)	11 (1.2%)	187 (0.9%)	872 (0.8%)	1,880 (1.0%)	2,800 (1.4%)	2,567 (1.6%)	1,393 (1.7%)	618 (1.9%)	10,341 (1.3%)
<b>Urinary stones</b>	7 (0.9%)	6 (0.7%)	116 (0.6%)	591 (0.6%)	1,502 (0.8%)	2,216 (1.1%)	2,352 (1.4%)	1,186 (1.5%)	428 (1.3%)	8,404 (1.1%)
<b>Ischemic heart disease</b>	16 (2.0%)	12 (1.3%)	246 (1.2%)	1,320 (1.2%)	3,162 (1.7%)	4,601 (2.3%)	4,029 (2.5%)	1,905 (2.4%)	715 (2.2%)	16,006 (2.0%)
<b>Heart failure</b>	11 (1.4%)	15 (1.7%)	198 (1.0%)	1,049 (1.0%)	2,348 (1.3%)	3,443 (1.7%)	3,124 (1.9%)	1,602 (2.0%)	690 (2.2%)	12,480 (1.6%)
<b>Cerebrovascular disease</b>	11 (1.4%)	9 (1.0%)	259 (1.3%)	1,505 (1.4%)	3,352 (1.8%)	4,331 (2.1%)	3,541 (2.2%)	1,667 (2.1%)	602 (1.9%)	15,277 (1.9%)
<b>Neurological disease</b>	85 (10.6%)	137 (15.2%)	2,481 (12.5%)	12,699 (11.8%)	22,561 (12.1%)	24,029 (11.8%)	18,788 (11.4%)	9,173 (11.5%)	3,641 (11.4%)	93,594 (11.8%)
<b>Parkinson's disease</b>	5 (0.6%)	9 (1.0%)	60 (0.3%)	241 (0.2%)	440 (0.2%)	470 (0.2%)	361 (0.2%)	162 (0.2%)	76 (0.2%)	1,824 (0.2%)
<b>Alzheimer's disease</b>	0 (0.0%)	0 (0.0%)	2 (0.0%)	14 (0.0%)	33 (0.0%)	41 (0.0%)	30 (0.0%)	14 (0.0%)	3 (0.0%)	137 (0.0%)
<b>Malignant</b>	0	1	28	117	155	82	36	17	2	438



tumor	(0.0%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.1%)
<b>Concomitant medication, n (%)</b>										
<b>Urate-lowering therapy</b>	1 (0.1%)	6 (0.7%)	111 (0.6%)	726 (0.7%)	3,308 (1.8%)	8,312 (4.1%)	9,260 (5.6%)	4,741 (5.9%)	2,338 (7.3%)	28,803 (3.6%)
<b>Anti-hypertensive drug</b>	80 (10.0%)	55 (6.1%)	961 (4.9%)	6,062 (5.6%)	15,890 (8.5%)	25,207 (12.4%)	24,052 (14.6%)	12,332 (15.4%)	4,825 (15.1%)	89,464 (11.2%)
<b>ACE inhibitors</b>	4 (0.5%)	2 (0.2%)	31 (0.2%)	206 (0.2%)	626 (0.3%)	1,078 (0.5%)	1,097 (0.7%)	552 (0.7%)	224 (0.7%)	3,820 (0.5%)
<b>ARB</b>	47 (5.9%)	36 (4.0%)	501 (2.5%)	3,221 (3.0%)	9,281 (5.0%)	15,840 (7.8%)	15,911 (9.7%)	8,467 (10.6%)	3,370 (10.6%)	56,674 (7.1%)
<b>Diuretic drug</b>	6 (0.8%)	2 (0.2%)	120 (0.6%)	612 (0.6%)	1,288 (0.7%)	1,891 (0.9%)	2,041 (1.2%)	1,310 (1.6%)	768 (2.4%)	8,038 (1.0%)
<b>Anti-diabetic drug</b>	19 (2.4%)	37 (4.1%)	508 (2.6%)	2,756 (2.6%)	6,447 (3.5%)	8,279 (4.1%)	6,079 (3.7%)	2,447 (3.1%)	804 (2.5%)	27,376 (3.4%)
<b>Anti-lipidemic drug</b>	54 (6.7%)	58 (6.4%)	956 (4.8%)	6,199 (5.8%)	15,392 (8.2%)	20,625 (10.1%)	17,002 (10.3%)	7,429 (9.3%)	2,472 (7.8%)	70,187 (8.8%)

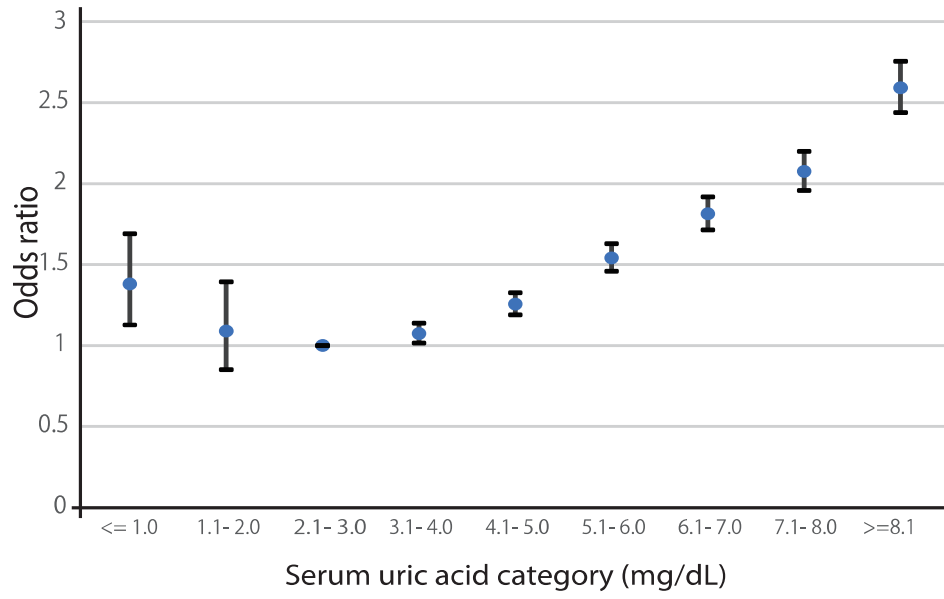
sUA, serum uric acid; SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

1,066,408 individuals with a serum uric acid level at least one data during medical check-ups between April 2018 and March 2019

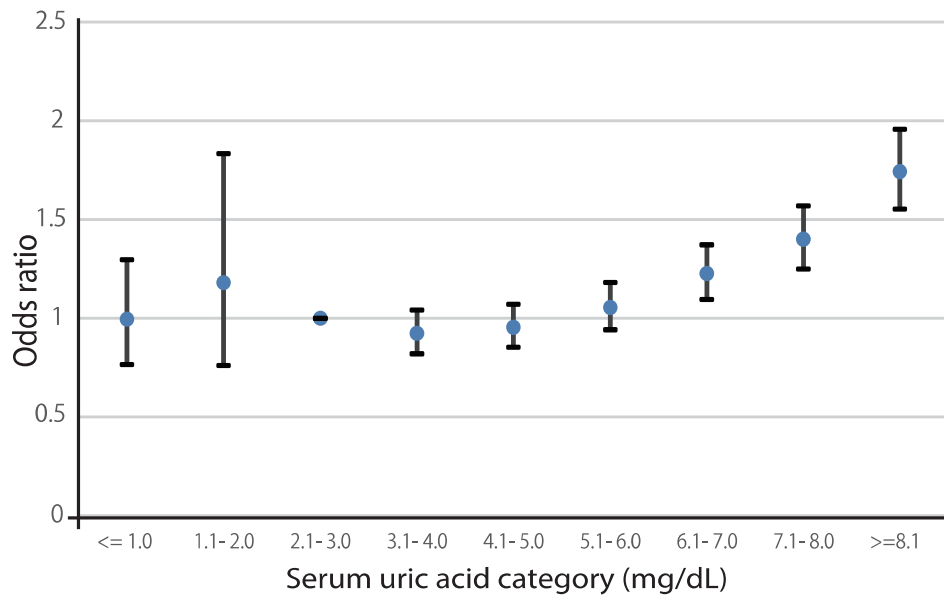
- A total of 269,900 individuals were excluded
- 13 individuals with a serum uric acid level exceeding 20.0 mg/dL
  - 27,099 individuals who had not been enrolled in insurance at least 6 months before the first check-up date
  - 242,788 individuals with missing data

796,508 subjects included in the analysis

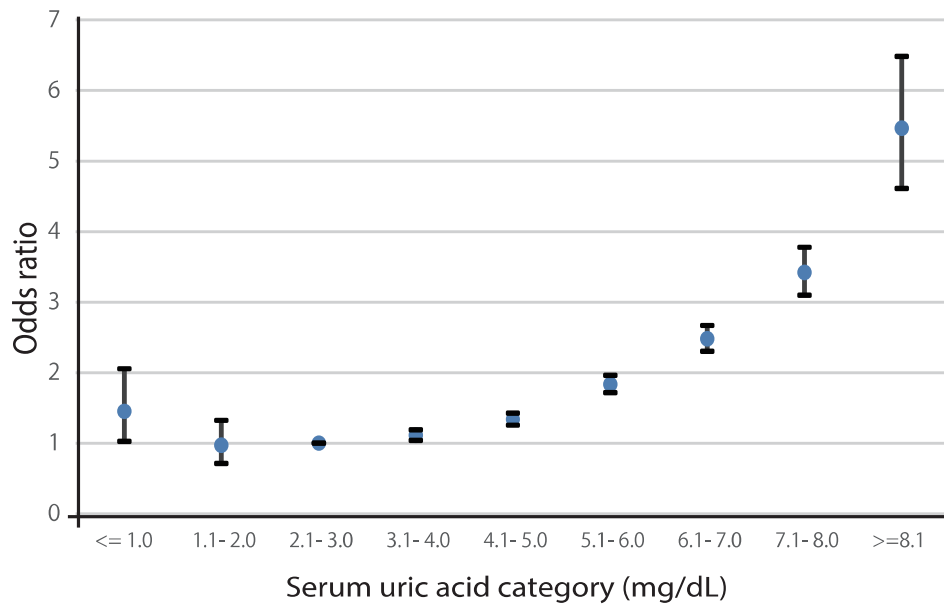
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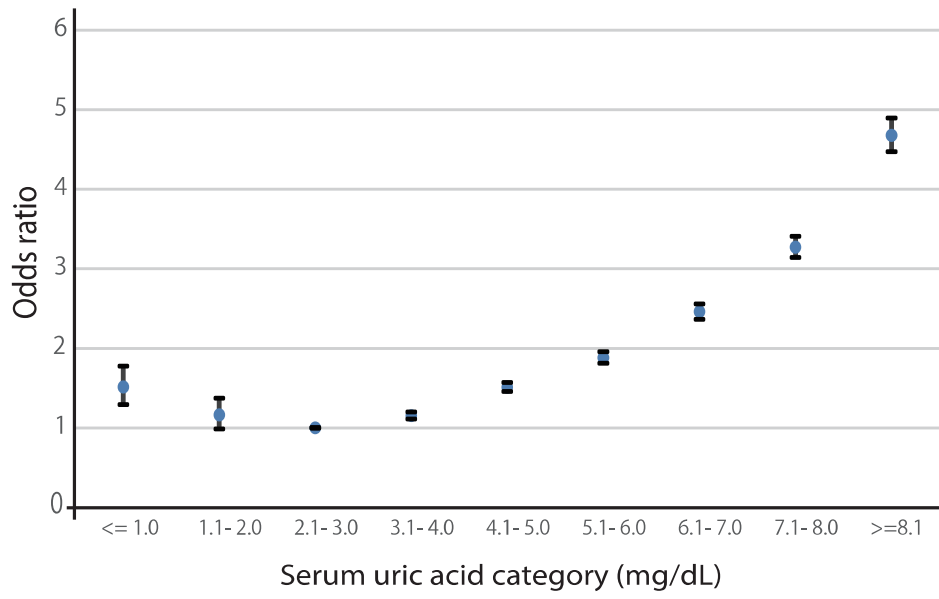
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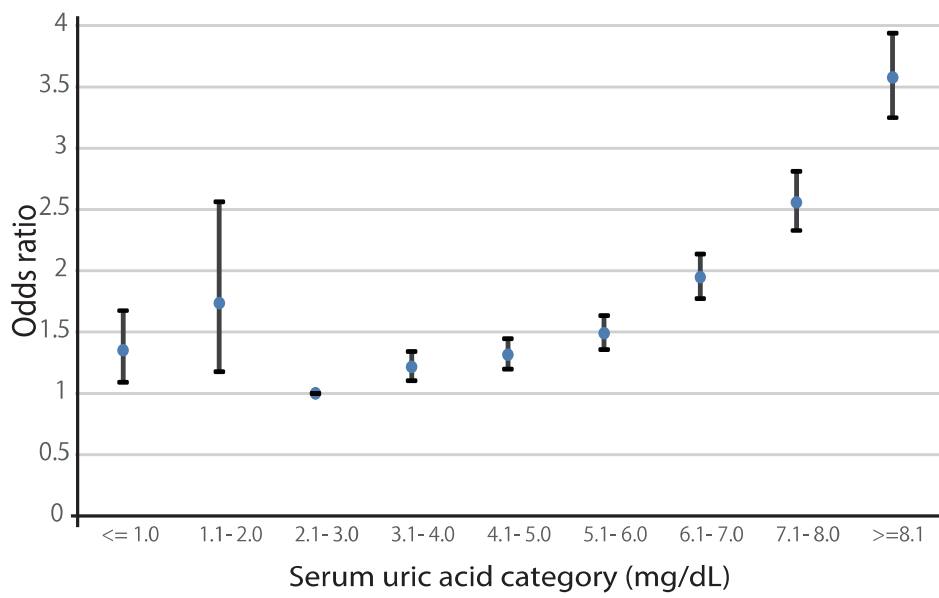
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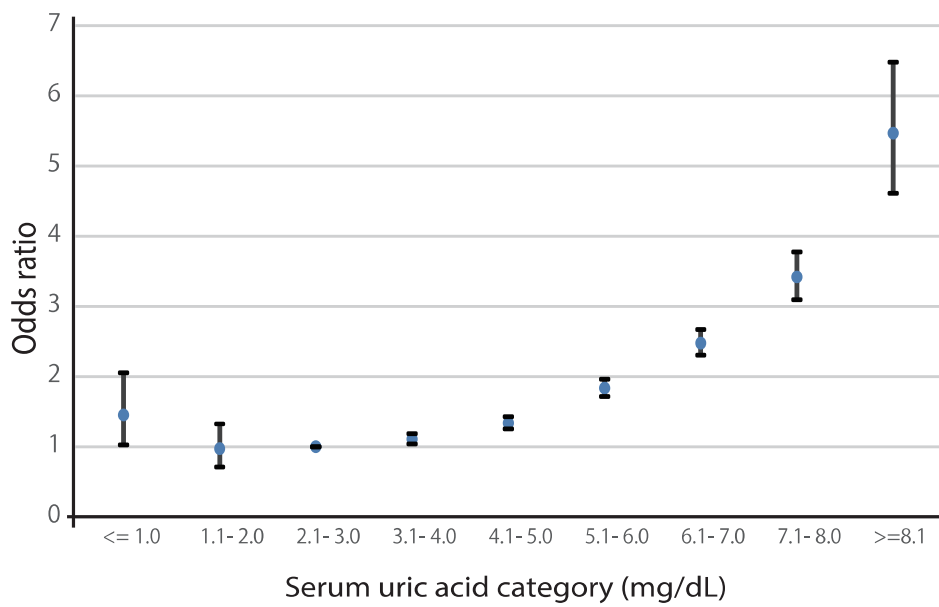
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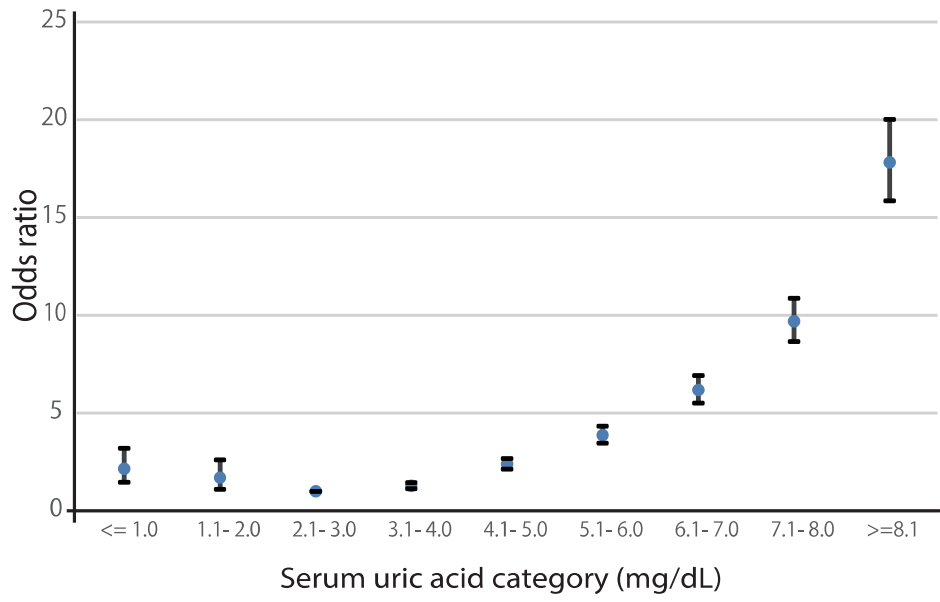
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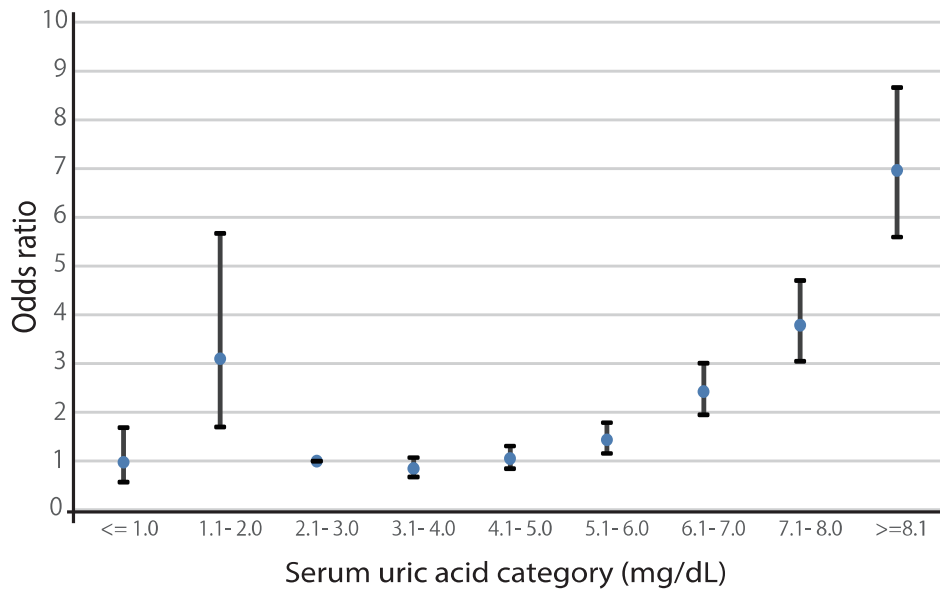
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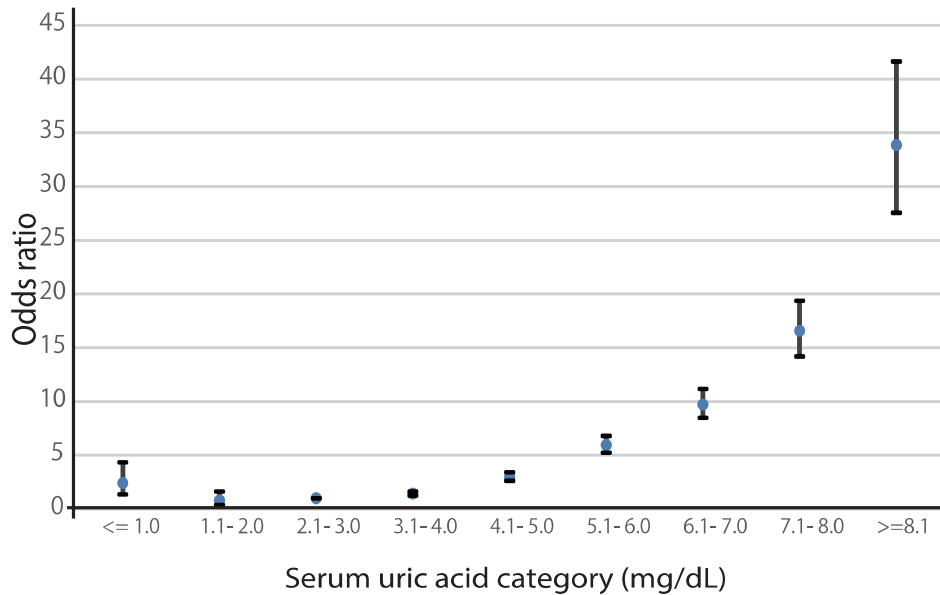
(a)



(b)



(c)



## Supplemental Digital Content

### The Association between Hypouricemia and Cardiometabolic Diseases: Analyzing Nationwide Data from Medical Check-up and Health Insurance Records

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33 the subgroup of patients with diabetes mellitus.

34

### 35 **Supplemental Figure**

36 Figure S1 Sex distribution of the overall population according to serum uric acid  
37 categories.

38

39

**Supplemental Tables**40 **Table S1** List of definitions.

<b>Pre-existing diseases</b>	<b>ICD-10 codes</b>
<b>Renal dysfunction</b>	N17-19, N26-28
<b>Urinary stones</b>	N20-23
<b>Ischemic heart disease</b>	I20-25
<b>Heart failure</b>	I50
<b>Cerebrovascular disease</b>	I60-69
<b>Neurological disease</b>	G00-99
<b>Parkinson's disease</b>	G20-22
<b>Alzheimer's disease</b>	G30
<b>Malignant tumour</b>	C00-97, D00-09
<b>History of medications</b>	<b>ATC codes</b>
<b>Urate-lowering therapy</b>	M04, except for colchicine
<b>Antihypertensive drug</b>	C02, C03, C07, C08, C09, C11
<b>ACE inhibitors</b>	C09A
<b>ARB</b>	C09C, C09D1, C09D3
<b>Diuretic drug</b>	C03
<b>Antidiabetic drug</b>	A10C, A10H, A10J, A10K, A10L, A10M, A10N, A10P, A10S, A10X
<b>Antilipidemic drug</b>	C10A, C10B, C11A

41

42 ICD-10, International Classification of Diseases 10<sup>th</sup> revision; ATC, anatomical therapeutic chemical;

43 ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker

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45



46 **Table S2** Male participant characteristics classified based on the serum uric acid  
 47 categories

	Serum uric acid category, mg/dL									Overall N=484,103
	<=1.0 N=472	1.1-2.0 N=126	2.1-3.0 N=2,277	3.1-4.0 N=17,415	4.1-5.0 N=62,878	5.1-6.0 N=145,137	6.1-7.0 N=148,237	7.1-8.0 N=76,488	8.1<= N=31,073	
Age, years, mean (SD)	44.8 (11.2)	47.9 (9.7)	46.1 (10.9)	45.7 (10.8)	45.4 (10.7)	44.7 (10.8)	44.6 (10.5)	44.6 (10.2)	43.9 (9.8)	44.7 (10.5)
BMI, kg/m <sup>2</sup> , mean (SD)	24.0 (3.5)	24.3 (4.6)	22.4 (3.2)	22.9 (3.4)	22.9 (3.4)	23.2 (3.3)	24.1 (3.5)	25.0 (3.7)	26.0 (4.1)	23.9 (3.6)
Waist circumference, cm, mean (SD)	84.5 (9.7)	84.9 (11.4)	80.3 (9.0)	81.6 (9.4)	81.5 (9.4)	82.5 (9.1)	84.9 (9.3)	87.3 (9.6)	89.9 (10.3)	84.3 (9.7)
Smoking, n (%)	162 (34.3%)	44 (34.9%)	856 (37.6%)	6,388 (36.7%)	22,940 (36.5%)	50,606 (34.9%)	50,427 (34.0%)	26,197 (34.3%)	11,433 (36.8%)	169,053 (34.9%)
Drinking habits, n (%)	308 (65.3%)	76 (60.3%)	1,378 (60.5%)	10,817 (62.1%)	38,463 (61.2%)	94,766 (65.3%)	103,981 (70.2%)	56,227 (73.5%)	23,274 (74.9%)	329,290 (68.0%)
Serum uric acid, mg/dL, mean (SD)	0.7 (0.2)	1.6 (0.3)	2.8 (0.2)	3.7 (0.3)	4.6 (0.3)	5.6 (0.3)	6.5 (0.3)	7.5 (0.3)	8.7 (0.7)	6.2 (1.2)
eGFR, mL/min/1.73m <sup>2</sup> , mean (SD)	82.2 (14.2)	77.1 (21.7)	84.9 (18.6)	83.6 (16.0)	82.8 (15.0)	80.8 (14.2)	78.1 (14.0)	75.8 (14.1)	73.5 (14.7)	79.1 (14.6)
History of disease, n (%)										
Renal dysfunction	12 (2.5%)	7 (5.6%)	63 (2.8%)	294 (1.7%)	899 (1.4%)	2,007 (1.4%)	2,195 (1.5%)	1,262 (1.7%)	572 (1.8%)	7,311 (1.5%)
Urinary stones	5 (1.1%)	1 (0.8%)	28 (1.2%)	179 (1.0%)	886 (1.4%)	1,879 (1.3%)	2,193 (1.5%)	1,142 (1.5%)	416 (1.3%)	6,729 (1.4%)
Ischemic heart disease	12 (2.5%)	6 (4.8%)	89 (3.9%)	547 (3.1%)	1,740 (2.8%)	3,592 (2.5%)	3,608 (2.4%)	1,781 (2.3%)	691 (2.2%)	12,066 (2.5%)
Heart failure	10 (2.1%)	4 (3.2%)	79 (3.5%)	401 (2.3%)	1,243 (2.0%)	2,578 (1.8%)	2,775 (1.9%)	1,464 (1.9%)	641 (2.1%)	9,195 (1.9%)
Cerebrovascular disease	10 (2.1%)	2 (1.6%)	62 (2.7%)	435 (2.5%)	1,527 (2.4%)	3,046 (2.1%)	3,085 (2.1%)	1,521 (2.0%)	571 (1.8%)	10,259 (2.1%)
Neurological disease	51 (10.8%)	24 (19.1%)	313 (13.8%)	2,167 (12.4%)	7,263 (11.6%)	15,808 (10.9%)	16,170 (10.9%)	8,475 (11.1%)	3,459 (11.1%)	53,730 (11.1%)
Parkinson's disease	5 (1.1%)	3 (2.4%)	9 (0.4%)	48 (0.3%)	159 (0.3%)	284 (0.2%)	273 (0.2%)	135 (0.2%)	67 (0.2%)	983 (0.2%)
Alzheimer's disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.0%)	17 (0.0%)	24 (0.0%)	26 (0.0%)	12 (0.0%)	2 (0.0%)	83 (0.0%)
Malignant tumor	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.0%)	9 (0.0%)	14 (0.0%)	20 (0.0%)	13 (0.0%)	0 (0.0%)	60 (0.0%)
Concomitant medication, n (%)										
Urate-lowering therapy	1 (0.2%)	5 (4.0%)	96 (4.2%)	688 (4.0%)	3,171 (5.0%)	8,085 (5.6%)	9,084 (6.1%)	4,672 (6.1%)	2,292 (7.4%)	28,094 (5.8%)
Anti-hypertensive drug	58 (12.3%)	27 (21.4%)	324 (14.2%)	2,288 (13.1%)	8,079 (12.9%)	18,403 (12.7%)	20,871 (14.1%)	11,351 (14.8%)	4,573 (14.7%)	65,974 (13.6%)
ACE inhibitors	4 (0.9%)	2 (1.6%)	15 (0.7%)	117 (0.7%)	428 (0.7%)	865 (0.6%)	989 (0.7%)	521 (0.7%)	206 (0.7%)	3,147 (0.7%)
ARB	35 (7.4%)	21 (16.7%)	191 (8.4%)	1,457 (8.4%)	5,196 (8.3%)	11,983 (8.3%)	13,823 (9.4%)	7,795 (10.2%)	3,200 (10.3%)	43,801 (9.1%)
Diuretic drug	3 (0.6%)	0 (0.0%)	31 (1.4%)	165 (1.0%)	564 (0.9%)	1,231 (0.9%)	1,673 (1.1%)	1,151 (1.5%)	691 (2.2%)	5,509 (1.1%)
Anti-diabetic drug	16 (3.4%)	17 (13.5%)	240 (10.5%)	1,623 (9.3%)	4,740 (7.5%)	7,066 (4.9%)	5,472 (3.7%)	2,276 (3.0%)	754 (2.4%)	22,204 (4.6%)
Anti-lipidemic drug	37 (7.8%)	23 (18.3%)	256 (11.2%)	2,073 (11.9%)	7,197 (11.5%)	14,608 (10.1%)	14,610 (9.9%)	6,834 (8.9%)	2,342 (7.5%)	47,980 (9.9%)

48

49 SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated

50 glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor

51 blocker.

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54 **Table S3** Female participant characteristics classified based on the serum uric acid  
 55 categories

	Serum uric acid category, mg/dL									Overall N=312,405
	≤1.0 N=331	1.1–2.0 N=775	2.1–3.0 N=17,550	3.1–4.0 N=90,412	4.1–5.0 N=124,147	5.1–6.0 N=58,574	6.1–7.0 N=16,267	7.1–8.0 N=3,535	8.1+ N=814	
Age, years, mean (SD)	45.0 (10.0)	41.8 (8.6)	42.5 (9.2)	43.0 (9.6)	44.4 (10.3)	46.6 (10.6)	48.6 (10.3)	49.1 (9.9)	48.0 (10.5)	44.6 (10.2)
BMI, kg/m <sup>2</sup> , mean (SD)	21.8 (3.5)	20.4 (2.7)	20.5 (2.8)	20.8 (2.9)	21.6 (3.4)	23.2 (4.1)	25.0 (4.9)	26.4 (5.6)	26.7 (6.4)	21.8 (3.7)
Waist circumference, cm, mean (SD)	77.5 (9.5)	73.5 (7.9)	74.0 (7.8)	74.7 (8.0)	77.0 (9.0)	81.2 (10.3)	85.8 (11.5)	89.2 (12.6)	89.7 (14.1)	77.6 (9.7)
Smoking, n (%)	25 (7.6%)	67 (8.7%)	1,453 (8.3%)	7,436 (8.2%)	10,519 (8.5%)	5,995 (10.2%)	2,035 (12.5%)	551 (15.6%)	134 (16.5%)	28,215 (9.0%)
Drinking habits, n (%)	147 (44.4%)	263 (33.9%)	6,423 (36.6%)	35,690 (39.5%)	54,669 (44.0%)	27,723 (47.3%)	8,057 (49.5%)	1,727 (48.9%)	397 (48.8%)	135,096 (43.2%)
Serum uric acid, mg/dL, mean (SD)	0.6 (0.1)	1.8 (0.2)	2.7 (0.3)	3.6 (0.3)	4.5 (0.3)	5.5 (0.3)	6.4 (0.3)	7.4 (0.3)	8.7 (0.8)	4.5 (1.0)
eGFR, mL/min/1.73m <sup>2</sup> , mean (SD)	81.8 (14.3)	93.8 (21.2)	88.9 (16.5)	85.5 (15.3)	80.9 (14.8)	76.9 (14.8)	73.7 (15.3)	70.8 (16.6)	67.0 (19.0)	81.4 (15.7)
<b>History of disease, n (%)</b>										
Renal dysfunction	1 (0.3%)	4 (0.5%)	124 (0.7%)	578 (0.6%)	981 (0.8%)	793 (1.4%)	372 (2.3%)	131 (3.7%)	46 (5.7%)	3,030 (1.0%)
Urinary stones	2 (0.6%)	5 (0.7%)	88 (0.5%)	412 (0.5%)	616 (0.5%)	337 (0.6%)	159 (1.0%)	44 (1.2%)	12 (1.5%)	1,675 (0.5%)
Ischemic heart disease	4 (1.2%)	6 (0.8%)	157 (0.9%)	773 (0.9%)	1,422 (1.2%)	1,009 (1.7%)	421 (2.6%)	124 (3.5%)	24 (3.0%)	3,940 (1.3%)
Heart failure	1 (0.3%)	11 (1.4%)	119 (0.7%)	648 (0.7%)	1,105 (0.9%)	865 (1.5%)	349 (2.2%)	138 (3.9%)	49 (6.0%)	3,285 (1.1%)
Cerebrovascular disease	1 (0.3%)	7 (0.9%)	197 (1.1%)	1,070 (1.2%)	1,825 (1.5%)	1,285 (2.2%)	456 (2.8%)	146 (4.1%)	31 (3.8%)	5,018 (1.6%)
Neurological disease	34 (10.3%)	113 (14.6%)	2,168 (12.4%)	10,532 (11.7%)	15,298 (12.3%)	8,221 (14.0%)	2,618 (16.1%)	698 (19.8%)	182 (22.4%)	39,864 (12.8%)
Parkinson's disease	0 (0.0%)	6 (0.8%)	51 (0.3%)	193 (0.2%)	281 (0.2%)	186 (0.3%)	88 (0.5%)	27 (0.8%)	9 (1.1%)	841 (0.3%)
Alzheimer's disease	0 (0.0%)	0 (0.0%)	2 (0.0%)	12 (0.0%)	16 (0.0%)	17 (0.0%)	4 (0.0%)	2 (0.1%)	1 (0.1%)	54 (0.0%)
Malignant tumor	0 (0.0%)	1 (0.1%)	28 (0.2%)	113 (0.1%)	146 (0.1%)	68 (0.1%)	16 (0.1%)	4 (0.1%)	2 (0.3%)	378 (0.1%)
<b>Concomitant medication, n (%)</b>										
Urate-lowering therapy	0 (0.0%)	1 (0.1%)	15 (0.1%)	38 (0.0%)	137 (0.1%)	227 (0.4%)	176 (1.1%)	69 (2.0%)	46 (5.7%)	709 (0.2%)
Anti-hypertensive drug	22 (6.7%)	28 (3.6%)	637 (3.6%)	3,774 (4.2%)	7,811 (6.3%)	6,804 (11.6%)	3,181 (19.6%)	981 (27.8%)	252 (31.0%)	23,490 (7.5%)
ACE inhibitors	0 (0.0%)	0 (0.0%)	16 (0.1%)	89 (0.1%)	198 (0.2%)	213 (0.4%)	108 (0.7%)	31 (0.9%)	18 (2.2%)	673 (0.2%)
ARB	12 (3.6%)	15 (1.9%)	310 (1.8%)	1,764 (2.0%)	4,085 (3.3%)	3,857 (6.6%)	1,988 (12.2%)	672 (19.0%)	170 (20.9%)	12,873 (4.1%)
Diuretic drug	3 (0.9%)	2 (0.3%)	89 (0.5%)	447 (0.5%)	724 (0.6%)	660 (1.1%)	368 (2.3%)	159 (4.5%)	77 (9.5%)	2,529 (0.8%)
Anti-diabetic drug	3 (0.9%)	20 (2.6%)	268 (1.5%)	1,133 (1.3%)	1,707 (1.4%)	1,213 (2.1%)	607 (3.7%)	171 (4.8%)	50 (6.1%)	5,172 (1.7%)
Anti-lipidemic drug	17 (5.1%)	35 (4.5%)	700 (4.0%)	4,126 (4.6%)	8,195 (6.6%)	6,017 (10.3%)	2,392 (14.7%)	595 (16.8%)	130 (16.0%)	22,207 (7.1%)

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57 SD, standard deviation; BMI, body mass index; IQR, interquartile range; eGFR, estimated

58 glomerular filtration rate; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor

59 blocker.

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66 **Table S4** Frequency of cardiometabolic comorbidities for each serum uric acid  
 67 category

	Serum uric acid category, mg/dL																			
	<=1.0		1.1-2.0		2.1-3.0		3.1-4.0		4.1-5.0		5.1-6.0		6.1-7.0		7.1-8.0		8.1<=		overall	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<b>Total</b>	803		901		19,827		107,827		187,025		203,711		164,504		80,023		31,887		796,508	
<b>Hypertension</b>	157	(19.6)	92	(10.2)	1,795	(9.1)	11,509	(10.7)	29,316	(15.7)	46,018	(22.6)	45,532	(27.7)	25,466	(31.8)	11,719	(36.8)	171,604	(21.5)
<b>Dyslipidemia</b>	304	(37.9)	218	(24.2)	4,200	(21.2)	26,775	(24.8)	63,807	(34.1)	89,135	(43.8)	86,476	(52.6)	48,896	(61.1)	22,353	(70.1)	342,164	(43.0)
<b>Reduced kidney function</b>	31	(3.9)	24	(2.7)	342	(1.7)	2,471	(2.3)	8,432	(4.5)	13,032	(6.4)	13,856	(8.4)	9,048	(11.3)	5,196	(16.3)	52,432	(6.6)
<b>Diabetes mellitus</b>	33	(4.1)	47	(5.2)	678	(3.4)	3,729	(3.5)	9,139	(4.9)	12,429	(6.1)	9,796	(6.0)	4,359	(5.5)	1,625	(5.1)	41,835	(5.3)
<b>Male</b>	472		126		2,277		17,415		62,878		145,137		148,237		76,488		31,073		484,103	
<b>Hypertension</b>	112	(23.7)	40	(31.8)	546	(24.0)	3,944	(22.7)	14,046	(22.3)	33,588	(23.1)	40,191	(27.1)	23,940	(31.3)	11,305	(36.4)	127,712	(26.4)
<b>Dyslipidemia</b>	207	(43.9)	67	(53.2)	810	(35.6)	6,979	(40.1)	25,853	(41.1)	63,449	(43.7)	77,180	(52.1)	46,553	(60.8)	21,762	(70.0)	242,840	(50.2)
<b>Reduced kidney function</b>	18	(3.8)	16	(12.7)	99	(4.4)	600	(3.5)	2,511	(4.0)	7,132	(4.9)	11,200	(7.6)	8,195	(10.7)	4,907	(15.8)	34,678	(7.2)
<b>Diabetes mellitus</b>	26	(5.5)	24	(19.1)	333	(14.6)	2,201	(12.6)	6,585	(10.5)	10,299	(7.1)	8,672	(5.9)	4,007	(5.2)	1,530	(4.9)	33,677	(7.0)
<b>Female</b>	331		775		17,550		90,412		124,147		58,574		16,267		3,535		814		312,405	
<b>Hypertension</b>	45	(13.6)	52	(6.7)	1,249	(7.1)	7,565	(8.4)	15,270	(12.3)	12,430	(21.2)	5,341	(32.8)	1,526	(43.2)	414	(50.9)	43,892	(14.1)
<b>Dyslipidemia</b>	97	(29.3)	151	(19.5)	3,390	(19.3)	19,796	(21.9)	37,954	(30.6)	25,686	(43.9)	9,296	(57.2)	2,363	(66.9)	591	(72.6)	99,324	(31.8)
<b>Reduced kidney function</b>	13	(3.9)	8	(1.0)	243	(1.4)	1,871	(2.1)	5,921	(4.8)	5,900	(10.1)	2,656	(16.3)	853	(24.1)	289	(35.5)	17,754	(5.7)
<b>Diabetes mellitus</b>	7	(2.1)	23	(3.0)	345	(2.0)	1,528	(1.7)	2,554	(2.1)	2,130	(3.6)	1,124	(6.9)	352	(10.0)	95	(11.7)	8,158	(2.6)

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71 **Table S5** Crude and adjusted odds ratios and 95% confidence intervals for the  
 72 association between the serum uric acid levels and hypertension. (A)  
 73 Overall, (B) men, and (C) women

74 (A) Overall

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	2.44 (2.04–2.93)	1.38 (1.13–1.69)
		1.1–2.0 mg/dL	1.14 (0.92–1.43)	1.09 (0.85–1.39)
		3.1–4.0 mg/dL	1.20 (1.14–1.26)	1.07 (1.01–1.14)
		4.1–5.0 mg/dL	1.87 (1.78–1.96)	1.26 (1.19–1.33)
		5.1–6.0 mg/dL	2.93 (2.79–3.08)	1.54 (1.46–1.63)
		6.1–7.0 mg/dL	3.84 (3.66–4.04)	1.81 (1.71–1.92)
		7.1–8.0 mg/dL	4.69 (4.46–4.93)	2.07 (1.96–2.20)
		>=8.1 mg/dL	5.84 (5.53–6.16)	2.59 (2.44–2.75)
<b>Age</b> (per 10 year increase)			1.09 (1.09–1.09)	1.09 (1.08–1.09)
<b>Sex</b>	male		0.46 (0.45–0.46)	0.78 (0.77–0.79)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.39 (0.38–0.40)	0.65 (0.63–0.67)
		>=25.0 kg/m <sup>2</sup>	3.30 (3.26–3.34)	2.07 (2.03–2.11)
<b>Waist circumference</b>	normal	>=85 cm	3.67 (3.62–3.71)	1.47 (1.44–1.49)
<b>Smoke</b>			1.13 (1.11–1.14)	0.94 (0.93–0.95)
<b>Drinking habits</b>			1.43 (1.41–1.44)	1.29 (1.27–1.30)
<b>eGFR</b> (per 10 mL/min/1.73m <sup>2</sup> increase)			0.97 (0.97–0.97)	1.00 (1.00–1.00)
<b>Diabetes mellitus</b>			5.70 (5.59–5.81)	2.13 (2.08–2.18)
<b>Dyslipidemia</b>			2.82 (2.78–2.85)	1.28 (1.26–1.29)
<b>History of ischemic heart disease</b>			11.33 (10.93–11.75)	3.72 (3.56–3.88)
<b>History of heart failure</b>			12.18 (11.69–12.70)	4.70 (4.48–4.94)
<b>History of cerebrovascular disease</b>			6.17 (5.97–6.38)	2.44 (2.35–2.54)

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## 83 (B) Men

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	0.99 (0.78–1.25)	1.00 (0.76–1.30)
		1.1–2.0 mg/dL	1.48 (1.00–2.17)	1.18 (0.76–1.83)
		3.1–4.0 mg/dL	0.93 (0.84–1.03)	0.92 (0.82–1.04)
		4.1–5.0 mg/dL	0.91 (0.83–1.01)	0.96 (0.85–1.07)
		5.1–6.0 mg/dL	0.96 (0.87–1.05)	1.06 (0.94–1.18)
		6.1–7.0 mg/dL	1.18 (1.07–1.30)	1.23 (1.10–1.37)
		7.1–8.0 mg/dL	1.44 (1.31–1.59)	1.40 (1.25–1.57)
		>=8.1 mg/dL	1.81 (1.64–2.00)	1.74 (1.55–1.96)
<b>Age</b> (per 10 year increase)			1.09 (1.09–1.09)	1.08 (1.08–1.08)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.42 (0.40–0.44)	0.63 (0.60–0.67)
		>=25.0 kg/m <sup>2</sup>	2.87 (2.84–2.91)	2.02 (1.98–2.06)
<b>Waist circumference</b>	normal	>=85 cm	3.05 (3.01–3.09)	1.47 (1.45–1.50)
<b>Smoke</b>			0.87 (0.86–0.88)	0.94 (0.92–0.95)
<b>Drinking habits</b>			1.37 (1.35–1.39)	1.39 (1.37–1.41)
<b>eGFR</b> (per 10 mL/min/1.73m <sup>2</sup> increase)			0.97 (0.97–0.97)	1.00 (1.00–1.00)
<b>Diabetes mellitus</b>			4.63 (4.53–4.74)	2.06 (2.01–2.12)
<b>Dyslipidemia</b>			2.26 (2.23–2.29)	1.26 (1.24–1.28)
<b>History of ischemic heart disease</b>			11.49 (10.99–12.01)	3.78 (3.60–3.98)
<b>History of heart failure</b>			12.73 (12.08–13.42)	4.71 (4.43–5.00)
84 <b>History of cerebrovascular disease</b>			6.54 (6.27–6.82)	2.54 (2.42–2.67)

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## 87 (C) Women

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	2.05 (1.49–2.83)	1.45 (1.03–2.05)
		1.1–2.0 mg/dL	0.94 (0.70–1.25)	0.97 (0.71–1.33)
		3.1–4.0 mg/dL	1.19 (1.12–1.27)	1.11 (1.04–1.19)
		4.1–5.0 mg/dL	1.83 (1.72–1.94)	1.34 (1.25–1.43)
		5.1–6.0 mg/dL	3.52 (3.31–3.74)	1.84 (1.72–1.96)
		6.1–7.0 mg/dL	6.38 (5.97–6.82)	2.48 (2.30–2.67)
		7.1–8.0 mg/dL	9.91 (9.08–10.83)	3.42 (3.10–3.78)
		>=8.1 mg/dL	13.51 (11.64–15.68)	5.47 (4.61–6.48)
<b>Age (per 10-year increase)</b>			1.10 (1.10–1.11)	1.09 (1.09–1.09)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.52 (0.50–0.54)	0.68 (0.65–0.71)
		>=25.0 kg/m <sup>2</sup>	3.71 (3.63–3.80)	2.17 (2.10–2.25)
<b>Waist circumference</b>	normal	>=85 cm	4.03 (3.95–4.12)	1.41 (1.37–1.46)
<b>Smoke</b>			0.98 (0.95–1.02)	0.97 (0.93–1.01)
<b>Drinking habits</b>			0.93 (0.91–0.95)	1.11 (1.09–1.14)
<b>eGFR (per 10-mL/min/1.73m<sup>2</sup> increase)</b>			0.97 (0.97–0.97)	1.00 (1.00–1.01)
<b>Diabetes mellitus</b>			7.45 (7.13–7.80)	2.29 (2.18–2.41)
<b>Dyslipidemia</b>			3.46 (3.39–3.53)	1.27 (1.24–1.31)
<b>History of ischemic heart disease</b>			9.44 (8.85–10.07)	3.55 (3.29–3.84)
<b>History of heart failure</b>			10.26 (9.56–11.02)	4.60 (4.23–5.01)
88 <b>History of cerebrovascular disease</b>			5.66 (5.35–5.99)	2.24 (2.10–2.40)

89 OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular  
90 filtration rate.

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92 **Table S6** Crude and adjusted odds ratios and 95% confidence intervals for the  
 93 association between the serum uric acid levels and dyslipidemia. (A)  
 94 Overall, (B) men, and (C) women

95 (A) Overall

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	2.27 (1.96–2.63)	1.52 (1.30–1.78)
		1.1–2.0 mg/dL	1.19 (1.02–1.39)	1.16 (0.98–1.38)
		3.1–4.0 mg/dL	1.23 (1.19–1.28)	1.16 (1.11–1.20)
		4.1–5.0 mg/dL	1.93 (1.86–2.00)	1.51 (1.46–1.57)
		5.1–6.0 mg/dL	2.90 (2.79–3.00)	1.88 (1.81–1.96)
		6.1–7.0 mg/dL	4.12 (3.98–4.27)	2.46 (2.37–2.56)
		7.1–8.0 mg/dL	5.85 (5.63–6.06)	3.27 (3.14–3.41)
		>=8.1 mg/dL	8.72 (8.37–9.09)	4.68 (4.47–4.90)
<b>Age (per 10 year increase)</b>			1.05 (1.05–1.05)	1.05 (1.05–1.05)
<b>Sex</b>	male		0.46 (0.46–0.47)	0.84 (0.83–0.85)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.33 (0.32–0.33)	0.49 (0.48–0.50)
		>=25.0 kg/m <sup>2</sup>	3.29 (3.26–3.33)	1.64 (1.62–1.67)
<b>Waist circumference</b>	normal	>=85 cm	3.78 (3.74–3.82)	1.73 (1.71–1.76)
<b>Smoke</b>			1.38 (1.36–1.39)	1.15 (1.13–1.16)
<b>Drinking habits</b>			0.99 (0.98–1.00)	0.73 (0.73–0.74)
<b>Diabetes mellitus</b>			4.63 (4.52–4.74)	1.95 (1.90–2.00)
<b>Hypertension</b>			2.82 (2.78–2.85)	1.20 (1.18–1.21)
<b>History of ischemic heart disease</b>			3.93 (3.79–4.07)	1.67 (1.60–1.74)
<b>History of heart failure</b>			2.93 (2.82–3.04)	1.11 (1.07–1.16)
96 <b>History of cerebrovascular disease</b>			3.41 (3.29–3.53)	1.69 (1.63–1.76)

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108 (B) Men

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	≤1.0 mg/dL	1.42 (1.16–1.73)	1.35 (1.09–1.67)
		1.1–2.0 mg/dL	2.06 (1.43–2.95)	1.74 (1.18–2.56)
		3.1–4.0 mg/dL	1.21 (1.11–1.33)	1.22 (1.10–1.34)
		4.1–5.0 mg/dL	1.27 (1.16–1.38)	1.32 (1.20–1.45)
		5.1–6.0 mg/dL	1.41 (1.29–1.53)	1.49 (1.36–1.63)
		6.1–7.0 mg/dL	1.97 (1.80–2.15)	1.95 (1.77–2.14)
		7.1–8.0 mg/dL	2.81 (2.58–3.07)	2.56 (2.33–2.81)
		≥8.1 mg/dL	4.23 (3.87–4.63)	3.58 (3.25–3.94)
<b>Age (per 10 year increase)</b>			1.04 (1.04–1.04)	1.03 (1.03–1.03)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.26 (0.25–0.27)	0.35 (0.33–0.36)
		≥25.0 kg/m <sup>2</sup>	3.03 (3.00–3.07)	1.64 (1.61–1.67)
<b>Waist circumference</b>	normal	≥85 cm	3.26 (3.22–3.30)	1.77 (1.74–1.80)
<b>Smoke</b>			1.09 (1.08–1.11)	1.15 (1.14–1.17)
<b>Drinking habits</b>			0.88 (0.87–0.89)	0.79 (0.78–0.80)
<b>Diabetes mellitus</b>			3.48 (3.40–3.58)	1.94 (1.89–2.00)
<b>Hypertension</b>			2.26 (2.23–2.29)	1.21 (1.19–1.22)
<b>History of ischemic heart disease</b>			3.54 (3.39–3.69)	1.82 (1.73–1.91)
<b>History of heart failure</b>			2.61 (2.49–2.73)	1.14 (1.08–1.20)
<b>History of cerebrovascular disease</b>			2.87 (2.74–3.00)	1.57 (1.50–1.65)

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## 111 (C) Women

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	≤1.0 mg/dL	1.73 (1.36–2.20)	1.29 (0.99–1.68)
		1.1–2.0 mg/dL	1.01 (0.84–1.21)	1.09 (0.89–1.32)
		3.1–4.0 mg/dL	1.17 (1.12–1.22)	1.11 (1.06–1.16)
		4.1–5.0 mg/dL	1.84 (1.77–1.91)	1.47 (1.41–1.54)
		5.1–6.0 mg/dL	3.26 (3.13–3.40)	2.00 (1.91–2.09)
		6.1–7.0 mg/dL	5.57 (5.31–5.85)	2.62 (2.48–2.77)
		7.1–8.0 mg/dL	8.42 (7.78–9.12)	3.52 (3.22–3.85)
		≥8.1 mg/dL	11.07 (9.45–12.97)	5.43 (4.55–6.48)
<b>Age (per 10 year increase)</b>			1.09 (1.09–1.10)	1.08 (1.08–1.08)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.46 (0.45–0.48)	0.55 (0.54–0.57)
		≥25.0 kg/m <sup>2</sup>	2.74 (2.68–2.79)	1.67 (1.62–1.72)
<b>Waist circumference</b>	normal	≥85 cm	3.73 (3.66–3.80)	1.61 (1.56–1.65)
<b>Smoke</b>			1.03 (1.00–1.06)	1.06 (1.03–1.09)
<b>Drinking habits</b>			0.70 (0.69–0.71)	0.70 (0.69–0.71)
<b>Diabetes mellitus</b>			7.22 (6.86–7.61)	2.33 (2.20–2.47)
<b>Hypertension</b>			3.46 (3.39–3.53)	1.23 (1.20–1.27)
<b>History of ischemic heart disease</b>			3.89 (3.64–4.15)	1.47 (1.36–1.59)
<b>History of heart failure</b>			3.01 (2.81–3.23)	1.11 (1.02–1.21)
<b>History of cerebrovascular disease</b>			4.41 (4.16–4.68)	1.91 (1.79–2.04)

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113 OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular

114 filtration rate.

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116 **Table S7** Crude and adjusted odds ratios and their 95% confidence intervals for the  
 117 association between the serum uric acid levels and reduced renal function. (A)  
 118 Overall, (B) men, and (C) women

119 (A) Overall

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	2.29 (1.57–3.33)	2.17 (1.47–3.20)
		1.1–2.0 mg/dL	1.56 (1.03–2.37)	1.70 (1.10–2.62)
		3.1–4.0 mg/dL	1.34 (1.19–1.50)	1.29 (1.15–1.45)
		4.1–5.0 mg/dL	2.69 (2.41–3.00)	2.40 (2.14–2.68)
		5.1–6.0 mg/dL	3.89 (3.49–4.34)	3.88 (3.47–4.34)
		6.1–7.0 mg/dL	5.24 (4.70–5.84)	6.19 (5.53–6.93)
		7.1–8.0 mg/dL	7.26 (6.51–8.10)	9.70 (8.65–10.88)
		>=8.1 mg/dL	11.09 (9.93–12.39)	17.82 (15.86–20.03)
<b>Age (per 10 year increase)</b>			1.11 (1.11–1.11)	1.11 (1.11–1.11)
<b>Sex</b>	male		0.78 (0.77–0.80)	1.48 (1.44–1.52)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.65 (0.62–0.67)	0.99 (0.95–1.04)
		>=25.0 kg/m <sup>2</sup>	1.62 (1.59–1.65)	1.21 (1.18–1.24)
<b>Waist circumference</b>	normal	>=85 cm	1.74 (1.71–1.77)	0.84 (0.82–0.86)
<b>Smoke</b>			0.64 (0.62–0.65)	0.64 (0.62–0.65)
<b>Drinking habits</b>			0.93 (0.91–0.94)	0.76 (0.74–0.77)
<b>Diabetes mellitus</b>			2.24 (2.18–2.31)	1.02 (0.99–1.06)
<b>Dyslipidemia</b>			2.34 (2.30–2.38)	1.19 (1.16–1.21)
<b>Hypertension</b>			3.10 (3.04–3.16)	1.22 (1.19–1.24)
<b>History of renal dysfunction</b>			11.72 (11.26–12.20)	6.94 (6.63–7.26)
<b>History of heart failure</b>			4.14 (3.97–4.33)	1.43 (1.36–1.51)

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## 130 (B) Men

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	0.87 (0.52–1.46)	0.98 (0.57–1.68)
		1.1–2.0 mg/dL	3.20 (1.83–5.61)	3.10 (1.70–5.67)
		3.1–4.0 mg/dL	0.79 (0.63–0.98)	0.85 (0.67–1.07)
		4.1–5.0 mg/dL	0.92 (0.75–1.12)	1.05 (0.84–1.31)
		5.1–6.0 mg/dL	1.14 (0.93–1.39)	1.44 (1.16–1.79)
		6.1–7.0 mg/dL	1.80 (1.47–2.20)	2.42 (1.95–3.01)
		7.1–8.0 mg/dL	2.64 (2.16–3.23)	3.79 (3.05–4.71)
		>=8.1 mg/dL	4.13 (3.37–5.06)	6.96 (5.60–8.67)
<b>Age (per 10 year increase)</b>			1.11 (1.11–1.11)	1.11 (1.11–1.11)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.38 (0.34–0.42)	0.58 (0.52–0.65)
		>=25.0 kg/m <sup>2</sup>	1.63 (1.60–1.67)	1.29 (1.25–1.33)
<b>Waist circumference</b>	normal	>=85 cm	1.72 (1.69–1.76)	0.86 (0.83–0.89)
<b>Smoke</b>			0.53 (0.52–0.55)	0.61 (0.59–0.63)
<b>Drinking habits</b>			0.90 (0.88–0.92)	0.69 (0.67–0.71)
<b>Diabetes mellitus</b>			2.20 (2.13–2.27)	1.07 (1.03–1.11)
<b>Dyslipidemia</b>			2.08 (2.03–2.12)	1.25 (1.21–1.28)
<b>Hypertension</b>			3.22 (3.15–3.30)	1.33 (1.29–1.36)
<b>History of renal dysfunction</b>			13.17 (12.56–13.81)	7.74 (7.34–8.17)
<b>History of heart failure</b>			4.08 (3.88–4.29)	1.36 (1.29–1.44)

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134 (C) Women

	Reference	Category	Crude OR (95%CI)	Adjusted OR (95%CI)
<b>Serum uric acid caetgory</b>	2.1–3.0 mg/dL	<=1.0 mg/dL	2.91 (1.65–5.14)	2.43 (1.36–4.34)
		1.1–2.0 mg/dL	0.74 (0.37–1.51)	0.80 (0.39–1.64)
		3.1–4.0 mg/dL	1.51 (1.32–1.72)	1.43 (1.25–1.64)
		4.1–5.0 mg/dL	3.57 (3.13–4.06)	3.00 (2.62–3.41)
		5.1–6.0 mg/dL	7.98 (7.01–9.08)	5.95 (5.22–6.79)
		6.1–7.0 mg/dL	13.90 (12.16–15.88)	9.73 (8.49–11.16)
		7.1–8.0 mg/dL	22.65 (19.53–26.27)	16.58 (14.20–19.36)
		>=8.1 mg/dL	39.21 (32.38–47.48)	33.87 (27.55–41.63)
<b>Age (per 10 year increase)</b>			1.11 (1.11–1.12)	1.10 (1.10–1.10)
<b>BMI</b>	normal	<18.5 kg/m <sup>2</sup>	0.79 (0.76–0.83)	1.08 (1.02–1.13)
		>=25.0 kg/m <sup>2</sup>	1.44 (1.38–1.49)	0.97 (0.92–1.02)
<b>Waist circumference</b>	normal	>=85 cm	1.63 (1.57–1.68)	0.76 (0.72–0.80)
<b>Smoke</b>			0.83 (0.78–0.88)	0.84 (0.79–0.89)
<b>Drinking habits</b>			0.81 (0.79–0.84)	0.82 (0.80–0.85)
<b>Diabetes mellitus</b>			1.96 (1.82–2.11)	0.73 (0.67–0.79)
<b>Dyslipidemia</b>			2.75 (2.66–2.83)	1.11 (1.07–1.15)
<b>Hypertension</b>			2.71 (2.62–2.81)	0.98 (0.94–1.02)
<b>History of renal dysfunction</b>			8.16 (7.55–8.82)	4.81 (4.40–5.26)
<b>History of heart failure</b>			3.87 (3.54–4.23)	1.46 (1.32–1.62)

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136 OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular  
 137 filtration rate.

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139 **Table S8** Adjusted odds ratios and 95% confidence intervals for the association  
 140 between the serum uric acid levels and cardiometabolic comorbidities in  
 141 the subgroup of participants who did not receive drugs that decrease the  
 142 serum uric acid levels.

Cardiometabolic comorbidities	Serum uric acid category, mg/dL	Adjusted OR (95%CI)		
		Overall	Male	Female
<b>Hypertension</b>	<=1.0	1.55 (1.27–1.91)	1.17 (0.89–1.53)	1.48 (1.04–2.10)
	1.1–2.0	1.05 (0.81–1.36)	1.15 (0.71–1.86)	0.97 (0.71–1.33)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.11 (1.05–1.18)	0.98 (0.86–1.12)	1.13 (1.05–1.21)
	4.1–5.0	1.32 (1.25–1.40)	1.01 (0.90–1.15)	1.36 (1.28–1.45)
	5.1–6.0	1.65 (1.56–1.75)	1.13 (1.00–1.28)	1.88 (1.75–2.01)
	6.1–7.0	2.01 (1.90–2.13)	1.37 (1.22–1.55)	2.54 (2.36–2.74)
	7.1–8.0	2.39 (2.25–2.53)	1.63 (1.45–1.85)	3.50 (3.16–3.87)
	>=8.1	3.07 (2.88–3.27)	2.10 (1.85–2.38)	5.53 (4.64–6.58)
<b>Dyslipidemia</b>	<=1.0	1.56 (1.33–1.83)	1.43 (1.15–1.78)	1.30 (1.00–1.70)
	1.1–2.0	1.13 (0.95–1.34)	1.80 (1.20–2.72)	1.05 (0.86–1.28)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.16 (1.11–1.20)	1.23 (1.11–1.37)	1.11 (1.06–1.16)
	4.1–5.0	1.52 (1.47–1.58)	1.34 (1.21–1.48)	1.48 (1.41–1.54)
	5.1–6.0	1.91 (1.84–1.99)	1.53 (1.39–1.69)	2.00 (1.91–2.09)
	6.1–7.0	2.55 (2.45–2.65)	2.05 (1.86–2.26)	2.63 (2.49–2.78)
	7.1–8.0	3.42 (3.29–3.57)	2.72 (2.46–3.00)	3.50 (3.20–3.83)
	>=8.1	4.95 (4.73–5.19)	3.85 (3.48–4.25)	5.32 (4.44–6.38)
<b>Reduced renal function</b>	<=1.0	2.71 (1.82–4.05)	1.77 (0.98–3.18)	2.28 (1.25–4.16)
	1.1–2.0	1.59 (0.97–2.60)	4.50 (2.18–9.29)	0.74 (0.35–1.59)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.43 (1.26–1.62)	1.22 (0.89–1.68)	1.44 (1.26–1.66)
	4.1–5.0	2.68 (2.37–3.03)	1.41 (1.04–1.91)	3.00 (2.63–3.43)
	5.1–6.0	4.58 (4.05–5.17)	2.05 (1.52–2.77)	6.01 (5.26–6.87)
	6.1–7.0	7.86 (6.95–8.89)	3.86 (2.86–5.20)	9.78 (8.51–11.24)
	7.1–8.0	13.36 (11.79–15.13)	6.53 (4.84–8.81)	16.82 (14.37–19.70)
	>=8.1	25.64 (22.58–29.13)	12.54 (9.28–16.94)	33.32 (26.93–41.24)

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144 OR, odds ratio; CI, confidence interval

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146 **Table S9** Adjusted odds ratios and 95% confidence intervals for the association  
 147 between the serum uric acid levels and cardiometabolic comorbidities in  
 148 the subgroup of participants without diabetes mellitus

Cardiometabolic comorbidities	Serum uric acid category, mg/dL	Adjusted OR (95%CI)		
		Overall	Male	Female
<b>Hypertension</b>	<=1.0	1.46 (1.19–1.80)	0.97 (0.74–1.28)	1.55 (1.09–2.20)
	1.1–2.0	1.17 (0.90–1.51)	1.43 (0.88–2.31)	1.00 (0.72–1.38)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.06 (1.00–1.13)	0.85 (0.75–0.97)	1.11 (1.04–1.19)
	4.1–5.0	1.25 (1.18–1.33)	0.89 (0.78–1.01)	1.34 (1.25–1.43)
	5.1–6.0	1.54 (1.46–1.64)	0.97 (0.86–1.10)	1.85 (1.73–1.98)
	6.1–7.0	1.82 (1.72–1.93)	1.14 (1.00–1.29)	2.48 (2.30–2.68)
	7.1–8.0	2.09 (1.97–2.23)	1.31 (1.15–1.48)	3.52 (3.17–3.90)
	>=8.1	2.63 (2.47–2.81)	1.64 (1.44–1.87)	5.74 (4.80–6.86)
<b>Dyslipidemia</b>	<=1.0	1.58 (1.35–1.86)	1.46 (1.17–1.82)	1.33 (1.02–1.73)
	1.1–2.0	1.16 (0.97–1.38)	1.78 (1.17–2.72)	1.09 (0.89–1.33)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.16 (1.12–1.21)	1.26 (1.13–1.41)	1.11 (1.06–1.16)
	4.1–5.0	1.53 (1.47–1.59)	1.37 (1.23–1.52)	1.48 (1.41–1.54)
	5.1–6.0	1.92 (1.85–2.00)	1.56 (1.41–1.73)	2.01 (1.92–2.11)
	6.1–7.0	2.52 (2.42–2.63)	2.06 (1.86–2.28)	2.66 (2.51–2.81)
	7.1–8.0	3.38 (3.24–3.52)	2.72 (2.46–3.02)	3.61 (3.29–3.95)
	>=8.1	4.83 (4.61–5.07)	3.80 (3.42–4.22)	5.79 (4.81–6.96)
<b>Reduced renal function</b>	<=1.0	2.33 (1.56–3.48)	1.03 (0.59–1.81)	2.30 (1.26–4.21)
	1.1–2.0	1.66 (1.05–2.64)	3.88 (2.01–7.50)	0.73 (0.34–1.56)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.29 (1.14–1.46)	0.81 (0.62–1.05)	1.43 (1.24–1.64)
	4.1–5.0	2.46 (2.19–2.77)	1.00 (0.78–1.28)	3.01 (2.63–3.44)
	5.1–6.0	4.06 (3.61–4.57)	1.33 (1.04–1.70)	6.02 (5.26–6.88)
	6.1–7.0	6.49 (5.77–7.31)	2.24 (1.75–2.87)	9.81 (8.52–11.28)
	7.1–8.0	10.22 (9.06–11.52)	3.51 (2.74–4.49)	16.55 (14.11–19.43)
	>=8.1	18.80 (16.63–21.25)	6.46 (5.05–8.28)	33.05 (26.61–41.04)

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150 OR, odds ratio; CI, confidence interval

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158 **Table S10** Adjusted odds ratios and 95% confidence intervals for the association  
 159 between the serum uric acid levels and cardiometabolic comorbidities in  
 160 the subgroup of patients with diabetes mellitus

Cardiometabolic comorbidities	Serum uric acid category, mg/dL	Adjusted OR (95%CI)		
		Overall	Male	Female
<b>Hypertension</b>	<=1.0	0.64 (0.30–1.37)	0.72 (0.30–1.72)	0.38 (0.07–2.10)
	1.1–2.0	0.69 (0.35–1.35)	0.68 (0.28–1.66)	0.73 (0.26–2.01)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.16 (0.97–1.39)	1.22 (0.95–1.57)	1.10 (0.85–1.43)
	4.1–5.0	1.23 (1.04–1.46)	1.19 (0.93–1.51)	1.30 (1.01–1.68)
	5.1–6.0	1.40 (1.18–1.67)	1.33 (1.05–1.69)	1.53 (1.19–1.98)
	6.1–7.0	1.59 (1.34–1.90)	1.45 (1.14–1.85)	2.23 (1.70–2.94)
	7.1–8.0	1.72 (1.43–2.06)	1.58 (1.24–2.02)	2.29 (1.63–3.21)
	>=8.1	1.96 (1.60–2.40)	1.79 (1.37–2.32)	2.90 (1.71–4.93)
<b>Dyslipidemia</b>	<=1.0	0.71 (0.34–1.50)	0.70 (0.29–1.65)	0.48 (0.10–2.24)
	1.1–2.0	1.11 (0.57–2.15)	1.58 (0.56–4.41)	0.89 (0.36–2.21)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.14 (0.95–1.36)	1.02 (0.79–1.31)	1.22 (0.94–1.58)
	4.1–5.0	1.32 (1.12–1.57)	1.13 (0.88–1.44)	1.48 (1.16–1.91)
	5.1–6.0	1.41 (1.19–1.68)	1.20 (0.94–1.54)	1.59 (1.23–2.06)
	6.1–7.0	1.67 (1.41–1.99)	1.41 (1.11–1.80)	1.97 (1.48–2.62)
	7.1–8.0	1.77 (1.47–2.12)	1.47 (1.14–1.89)	2.34 (1.59–3.44)
	>=8.1	2.29 (1.85–2.85)	1.93 (1.46–2.55)	2.13 (1.17–3.89)
<b>Reduced renal function</b>	<=1.0	0.94 (0.19–4.75)	0.32 (0.04–2.92)	7.65 (0.81–72.44)
	1.1–2.0	1.91 (0.55–6.70)	1.38 (0.29–6.50)	2.83 (0.34–23.84)
	2.1–3.0	reference	reference	reference
	3.1–4.0	1.17 (0.79–1.74)	0.98 (0.60–1.58)	1.46 (0.72–2.93)
	4.1–5.0	1.65 (1.13–2.41)	1.23 (0.77–1.94)	2.54 (1.30–4.95)
	5.1–6.0	2.54 (1.75–3.69)	1.81 (1.15–2.85)	4.54 (2.34–8.81)
	6.1–7.0	4.30 (2.96–6.25)	3.06 (1.94–4.82)	8.03 (4.11–15.67)
	7.1–8.0	6.79 (4.65–9.92)	4.77 (3.02–7.54)	14.67 (7.29–29.53)
	>=8.1	12.88 (8.73–19.01)	9.00 (5.64–14.35)	33.12 (14.93–73.50)

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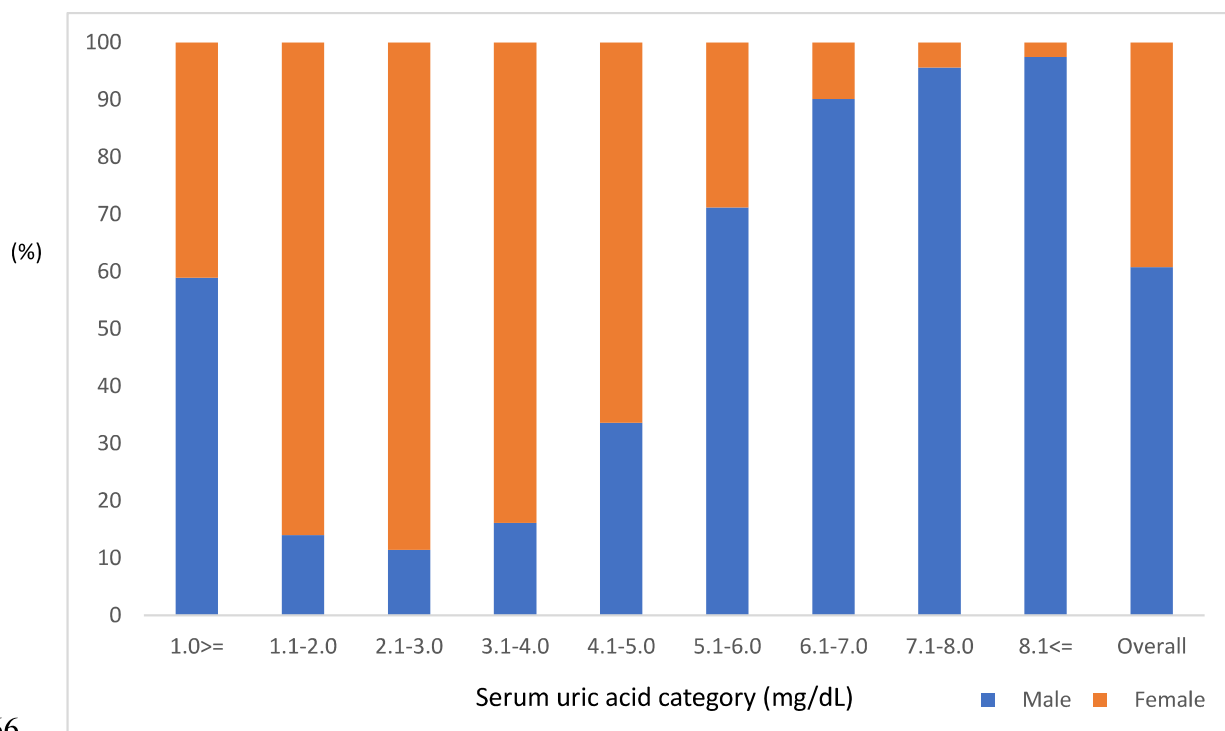
162 OR, odds ratio; CI, confidence interval

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## Supplemental Figure



166

167 **Figure S1** Sex distribution of the overall population according to the serum uric acid

168 categories

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