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# Cross-sectional association between gamma-glutamyl transferase and hyperuricaemia: the China Multi-Ethinic Cohort (CMEC) study

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## ABSTRACT

**Objectives** Several studies have demonstrated the association between gamma-glutamyl transferase (GGT) and hyperuricaemia, but little is known about such relation in less-developed ethnic minority regions.

**Design** We cross-sectionally analysed data from the China Multi-Ethnic Cohort (Yunnan region).

**Setting** Cross-sectional study.

**Participants** 22 020 participants aged 30–79 years from Han ethnicity, Yi ethnicity and Bai ethnicity.

**Outcomes** The serum level of uric acid, GGT and other metabolic parameters were tested. Weight, height and blood pressure were measured. Smoking, drinking, ethnicity, education and medical history were obtained from questionnaires.

**Results** In the crude model, compared with the lowest quintile, the second, third, fourth and fifth quintiles of serum GGT exhibited a positive association with hyperuricaemia risk (OR=1.69, 2.90, 4.34 and 7.70, 95% CI=1.42 to 2.01, 2.47 to 3.42, 3.71 to 5.09 and 6.60 to 8.98, respectively, p-trend<0.0001). In fully adjusted model, compared with the lowest quintile, the second, third, fourth and fifth quintiles of serum GGT also exhibited a positive association with hyperuricaemia risk (OR=1.26, 1.68, 2.02 and 3.02, 95% CI=1.04 to 1.51, 1.40 to 2.00, 1.69 to 2.42 and 2.51 to 3.64, respectively, p-trend<0.0001). Logistic regression model was conducted separately in ethnic groups. Compared with first quintile, the highest GGT level were related to higher risk of hyperuricaemia in three ethnic groups (OR (95% CI): 2.89 (2.26 to 3.68), 2.81 (1.93 to 4.11) and 3.04 (1.91 to 4.84) for Han, Yi and Bai ethnicity, respectively, p-trend <0.0001). The relationship between GGT and hyperuricaemia was also observed in different age groups or gender groups.

**Conclusions** High serum GGT level was related to a higher risk of hyperuricaemia in less-developed ethnic minority regions in China.

## Strengths and limitation of this study

⇒ This is the first epidemiological study to evaluate the association between gamma-glutamyl transferase and hyperuricaemia risk in less-developed ethnic minority regions.
⇒ The study investigated a large sample size of 22 020 and taking multiple covariate into consideration.
⇒ The cross-sectional nature of the study design makes it difficult to determine causal inference.
⇒ We do not consider the influence of diet.

## INTRODUCTION

In recent years, hyperuricaemia which has cast heavy health and economic burden to the world, has increased rapidly in the world-wide. hyperuricaemia was found in 14.6% of the US population, about 32.5 million individuals.[1] A study conducted in Adelaide showed that the prevalence of hyperuricaemia in South Australia is relatively high, with an overall prevalence of 16.6%.[2] Several epidemiological studies indicated that serum uric acids (SUA) had a detrimental effect on the prevalence of metabolic diseases, such as cardiovascular diseases,[3] metabolic syndrome.[4–6] Recent study found that serum gamma-glutamyl transferase (GGT) concentration were strongly related to elevated uric acid level in normotensive adults.[7]

GGT was widely presented throughout the body[8] and has been used as a marker of of non-alcoholic fatty liver disease.[9] A series of observational studies have indicated that increasing GGT levels could predict metabolic derangement such as obesity, diabetes and hypertension.[10–13] Recently, the association between increasing GGT level and SUA gained attention. However, the epidemiological results of the relationship between GGT levels and SUA are not consistent. Some literature showed that GGT is positively related to SUA,[5 7 14 15] while the other was not.[16] This may due to they only focused on special population like middle-aged and elderly females,[15] or normotensive adults[6] or only conducted with a small sample size.[5 14 16]

Despite the association between GGT and hyperuricaemia has been depicted, little is known about such associations in less-developed ethnic minority regions. The China Multi-Ethnic Cohort (CMEC) Study is a large-scale epidemiological study with great diversity in ethnicity.[17] Therefore, this study investigated whether serum GGT level were associated with hyperuricaemia in a large-scale Chinese general population in Yunnan, China. In addition, to elucidate the age, sex and ethnic difference affecting the relationship between serum GGT level and hyperuricaemia, we also was conducted separately in different age, gender and ethnic groups.

## METHODS

### Study participants

Data from the baseline survey of the CMEC Study (Yunnan region) were used for analysis. The details of the study design and methods have been described previously.[17] More than 20 000 Chinese population were recruited in Yunnan in this prospective cohort study. From 2018 to 2019, the survey was conducted in three cities by randomised sampling, including Lijiang City, Dali City and Chuxiong City. Participants were eligible for current study if they: (1) were 30–79 years old; (2) household registered in Yunnan province and residence for at least 1 year in the local area; (3) agree to participate and provide informed consent and (4) no mental illness, severe kidney diseases, tumour or other related diseases. Participants were excluded if: (1) refuse to provide written informed consent; (2) the subjects who had missing data on GGT level; (3) missing data on the determination of hyperuricaemia. Twenty-three thousand Chinese people were selected in the initial sampling, and a total of 23 143 subjects aged 30–79 were recruited at baseline. The final sample size for the present analysis was 22 020 (7242 males and 14778 females) after excluding unqualified samples. The informed consent form was read and signed by participants prior to this study. Ethical approval was received from the Kunming Medical University Medical Ethical Review Board.

### Assessment of GGT and SUA

Blood samples were obtained after participants fasted overnight. All blood samples were stored in vacuum tubes containing ethylenediaminetetraacetic acid. GGT level was determined using an autoanalyzer with the kinetic methods. Fasting blood samples were performed biochemical analyses on SUA using standard enzymatic method. We classified subjects as having hyperuricaemia if SUA above 7.0 mg/dL for males and above 6.0 mg/dL for females.[18] Recently, a new study had indicated that the level of SUA which was able to discriminate cardiovascular mortality status was 5.6 mg/dL,[19] so we also conducted a sensitive analysis by defining hyperuricaemia as SUA above 5.6 mg/dL. The results were showed in online supplemental file 1.

### Data collection

The explanatory variables in the study included age, sex, BMI, ethnicity (Han ethnicity, Yi ethnicity and Bai ethnicity), smoking status, drinking habit, education, hypertension, therapy for hypertension or other cardiovascular diseases (CVD), hyperglycaemia, triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), serum creatinine, daytime napping duration, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Anthropometric measurements were taken at baseline. Hypertension was defined as a systolic or diastolic blood pressure of ≥ 140/90 mm Hg or taking medication for antihypertensive medicine.[20] Electronic questionnaire was conducted to collect data. Concise question content and enhancing the degree of colloquialism could reduce disturbance of comprehension and increase compliance. Interviewers for the current study were local doctors and college students with medical backgrounds. Investigators with higher proficiency and higher educational level help to reduce response time of questions. The information was collected by a face-to-face interview implemented by these interviewers by local dialect. Also, preinvestigation was conducted before the survey. For data quality control, on the same day of data collection, the data quality inspectors drew random samples of questionnaires to assess their data quality by listening to the audio records. The sampling scheme was built on our computer system and could ensure that each interviewer was sampled at least once every 4 days. In surveys, interviewers are usually required to upload data on the day of the interview. After the data are transmitted back to the headquarters, the data will be merged immediately. Interviewers could receive feedback and guidance in time. The double data entry method was used and would be checked again. All data were stored and managed in electronic form by a self-developed computer system, with the central server located at the West China School of Public Health, Sichuan University. Different data sets were linked by the unique participant's ID. Current smokers were defined as ever smoking at least 100 during the lifetime. Drinking habit was defined as consuming alcohol at least once each week during preceding past half year. Education level were classified into six categories including (1) no formal education, (2) primary school, (3) junior high school, (4) high school, (5) upper high school and (6) college education or above. In the current study, higher education was defined as high school and above.

### Statistical analysis

Kolmogorov–Smirnov test was used to check the normality of continuous variables. Continuous variables were expressed as the mean±SD, and categorical variables were presented as frequencies and percentages. We compared characteristics of different GGT quintile categories using analysis of variance or the Kruskal-Wallis rank-sum test, and the $\chi^2$ test or Fisher's exact test for categorical variables. The prevalence of hyperuricaemia differing by age

or gender or ethnic groups was tested by $\chi^2$ test. Logistic regression models were used to calculated the ORs. The effect estimates were expressed as ORs and 95% CIs. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, ethnicity, education, smoking status, drinking habit, hypertension, hyperglycaemia, TG, LDL-c, HDL-c and serum creatinine. Model 3 was adjusted for age, sex, BMI, ethnicity, education, smoking status, drinking habit, hypertension, hyperglycaemia, TG, LDL-c, HDL-c, creatinine, daytime napping duration, therapy for hypertension or other CVD and ALT, AST. Sensitivity analysis was conducted by defining hyperuricaemia as SUA above 5.6 mg/dL. The statistical analyses were performed using SPSS V.21.0 for Windows (IBM Corporation), and the significance level was set as p<0.05.

### Patient and public involvement

Patients and the public were not involved in the development of research questions, design of the study, recruitment and conduct of the study or dissemination of the study results.

## RESULTS

Of the 22 020 participants, 3473 (15.8%) had hyperuricaemia. Males had a higher prevalence of hyperuricaemia (25.7%) than females (10.9%). The baseline characteristics of participants based on different serum GGT groups are presented in table 1. Participants with higher concentrations of serum GGT were more likely to be older, obese and to be male. Also, there were some factors that were significantly associated with serum GGT levels, including ethnicity, education, smoking status, drinking habit, hypertension, CVD, therapy for hypertension or other CVD, hyperglycaemic, TG, LDL-c, HDL-c, serum creatinine and ALT, AST (p<0.0001). We considered these potential confounding variables when evaluating the independent relationship between GGT and hyperuricaemia.

The prevalence of hyperuricaemia in all population and ORs (and 95% CIs) of the hyperuricaemia according to different serum GGT level were displayed in table 2. The prevalence of hyperuricaemia with different serum

**Table 1** Comparison of baseline characteristics according to quintiles of serum GGT among 22 020 participants

| Characteristics | GGT level | | | | | P value |
|---|---|---|---|---|---|---|
| | Q1 (n=3888) | Q2 (n=4711) | Q3 (n=4476) | Q4 (n=4475) | Q5 (n=4470) | |
| Age (years) | 49.2±10.3 | 51.6±10.7 | 53.5±10.2 | 54.2±10.1 | 54.0±10.0 | <0.0001 |
| Male gender (n, %) | 318 (8.2) | 1016 (21.6) | 1536 (34.3) | 1994 (44.6) | 2208 (49.4) | <0.0001 |
| BMI (kg/m²) | 21.8±2.8 | 22.3±3.1 | 22.9±3.2 | 23.6±3.6 | 24.2±3.4 | <0.0001 |
| Han ethnicity (n, %) | 1805 (46.4) | 2170 (46.1) | 2138 (47.8) | 1977 (44.2) | 1875 (41.9) | <0.0001 |
| Smoking (n, %) | 203 (5.2) | 711 (15.1) | 1128 (25.2) | 1434 (32.0) | 1610 (36.0) | <0.0001 |
| Drinking (n, %) | 470 (12.1) | 886 (18.8) | 1150 (25.7) | 1372 (30.7) | 1725 (38.6) | <0.0001 |
| Higher education (n, %) | 251 (6.5) | 309 (6.6) | 315 (7.0) | 319 (7.1) | 416 (9.3) | <0.0001 |
| Hypertension (n, %) | 630 (16.2) | 1012 (21.5) | 1205 (26.9) | 1442 (32.2) | 1559 (34.9) | <0.0001 |
| CVD (n, %) | 50 (1.3) | 101 (2.1) | 121 (2.7) | 135 (3.0) | 139 (3.1) | <0.0001 |
| Therapy for hypertension or other CVD (n, %) | 368 (9.5) | 653 (13.9) | 817 (18.3) | 923 (20.6) | 1024 (22.9) | <0.0001 |
| Hyperglycaemic (n, %) | 520 (13.4) | 872 (18.5) | 1036 (23.1) | 1279 (28.6) | 1483 (33.2) | <0.0001 |
| SUA (µmol/L)) | 256.7±63.8 | 280.4±70.6 | 303.8±78.7 | 325.1±88.5 | 352.8±98.0 | <0.0001 |
| Creatinine (µmol/L) | 69.7±14.3 | 73.6±21.9 | 76.5±17.6 | 79.1±19.4 | 81.0±23.1 | <0.0001 |
| TG (mmol/L) | 1.2±0.7 | 1.5±1.1 | 1.8±1.5 | 2.1±1.9 | 2.6±2.5 | <0.0001 |
| LDL-c (mmol/L) | 2.9±0.7 | 3.1±0.8 | 3.2±0.9 | 3.3±0.9 | 3.3±1.0 | <0.0001 |
| HDL-c (mmol/L) | 1.7±0.4 | 1.6±0.4 | 1.6±0.4 | 1.5±0.4 | 1.5±0.5 | <0.0001 |
| ALT (U/L) | 14.2±5.6 | 16.4±7.3 | 19.0±8.3 | 23.0±12.5 | 34.3±23.9 | <0.0001 |
| AST (U/L) | 22.2±5.9 | 23.3±6.4 | 24.5±7.1 | 26.3±9.3 | 32.1±17.5 | <0.0001 |
| AST: ALT ratio | 1.7±0.5 | 1.6±0.5 | 1.4±0.5 | 1.3±0.6 | 1.2±0.6 | <0.0001 |

Q1, quintile 1 (n = 3888): <15 U/L; Q2, quintile 2 (n = 4711): 15–21 U/L; Q3, quintile 3 (n = 4476): 21–30 U/L; Q4, quintile 4 (n = 4475): 30–50 U/L; Q5, quintile 5 (n = 4470): ≥ 50 U/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CVD, cardiovascular diseases; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SUA, serum uric acid; TG, triglycerides.

**Table 2** The prevalence of hyperuricaemia* and association of GGT level and hyperuricaemia in the participants

| GGT | Prevalence | | OR (95% CI) | P value | P for trend |
|---|---|---|---|---|---|
| Model 1 | | | | | <0.0001 |
| Q1 | 207 (5.3) | $X^2$=1260.6 | Reference | | |
| Q2 | 409 (8.7) | P<0.0001 | 1.69 (1.42 to 2.01) | <0.0001 | |
| Q3 | 628 (14.0) | | 2.90 (2.47 to 3.42) | <0.0001 | |
| Q4 | 878 (19.6) | | 4.34 (3.71 to 5.09) | <0.0001 | |
| Q5 | 1351 (30.2) | | 7.70 (6.60 to 8.98) | <0.0001 | |
| Model 2 | | | | | <0.0001 |
| Q1 | | | Reference | | |
| Q2 | | | 1.26 (1.05 to 1.52) | 0.01 | |
| Q3 | | | 1.70 (1.42 to 2.03) | <0.0001 | |
| Q4 | | | 2.05 (1.72 to 2.45) | <0.0001 | |
| Q5 | | | 3.12 (2.67 to 3.81) | <0.0001 | |
| Model 3 | | | | | <0.0001 |
| Q1 | | | Reference | | |
| Q2 | | | 1.26 (1.04 to 1.51) | 0.02 | |
| Q3 | | | 1.68 (1.40 to 2.00) | <0.0001 | |
| Q4 | | | 2.02 (1.69 to 2.42) | <0.0001 | |
| Q5 | | | 3.02 (2.51 to 3.64) | <0.0001 | |

Model 1: unadjusted.
Model 2: adjusted for age, sex, BMI, ethnicity, education, smoking status, drinking habits, hypertension, hyperglycaemic, TG, LDL-c, HDL-c and serum creatinine.
Model 3: adjusted for age, sex, BMI, ethnicity, education, smoking status, drinking habit, hypertension, hyperglycaemic, TG, LDL-c, HDL-c, serum creatinine, and daytime napping duration, therapy for hypertension or other cardiovascular diseases, ALT, AST.
*Hyperuricaemia was defined as serum uric acid above 7.0 mg/dL for males and above 6.0 mg/dL for females.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides.

GGT levels was 5.3%, 8.7%, 14.0%, 19.6% and 30.2%, respectively (p<0.0001). In the crude model, compared with the lowest quintile, the second, third, fourth and fifth quintiles of serum GGT exhibited a positive association with hyperuricaemia risk (OR=1.69, 2.90, 4.34 and 7.70, 95% CI=1.42 to 2.01, 2.47 to 3.42, 3.71 to 5.09 and 6.60 to 8.98, respectively, p-trend<0.0001). After adjustment for age, sex, BMI, ethnicity, education, smoking status, drinking habits, hypertension, hyperglycaemic, TG, LDL-c, HDL-c and creatinine (model 2), the associations decreased (OR=1.26, 1.70, 2.05 and 3.12, 95% CI=1.05 to 1.52, 1.42 to 2.0, 1.7 to 2.45 and 2.67 to 3.88, respectively, p-trend<0.0001). In fully adjusted model, compared with the lowest quintile, the second, third, fourth and fifth quintiles of serum GGT also exhibited a positive association with hyperuricaemia risk (OR=1.26, 1.68, 2.02 and 3.02, 95% CI=1.04 to 1.51, 1.40 to 2.00, 1.69 to 2.42 and 2.51 to 3.64, respectively, p-trend<0.0001).

To elucidate the sex difference affecting the relationship between serum GGT and hyperuricaemia, logistic regression model also was conducted separately in age and gender groups (table 3). For all age groups, those who were in fifth quintile had a higher odds of hyperuricaemia in fully adjusted model compared with those who were in first quintile (OR (95% CI): 3.32 (2.21 to 5.00) for age<45 years group; 3.06 (2.33 to 4.01) for 45–59 years group; 2.42 (1.75 to 3.36) for age>59 years group; p-trend<0.0001). The relationship between GGT and hyperuricaemia was observed both in males and females. For males, the highest level of GGTs were related to higher risk of hyperuricaemia (OR=2.65, 95% CI=1.79 to 3.91, p-trend<0.0001). For females, compared with first quintile, the third, forth and fifth were showed higher risk of hyperuricaemia (OR=1.72, 2.03 and 2.62, 95% CI=1.40 to 2.12, 1.64 to 2.52 and 2.09 to 3.28, respectively, p-trend<0.0001).

Table 4 displayed the prevalence of hyperuricaemia and association of GGT level with hyperuricaemia in the participants among different ethnic groups. The prevalence was 7.3%, 11.8%, 18.2%, 25.5% and 36.8% across five categories of GGT in Han ethnicity. The prevalence was 4.6%, 6.4%, 11.3%, 16.4% and 27.3% across five categories of GGT in Yi ethnicity. The prevalence was 2.8%, 5.7%, 9.0%, 13.5% and 22.6% across five categories of GGT in Bai ethnicity. Compared with first quintile, the highest GGT levels were related to higher risk of hyperuricaemia in three ethnic groups (OR (95% CI): 2.89 (2.26 to 3.68), 2.81 (1.93 to 4.11) and 3.04 (1.91 to 4.84) for Han, Yi and Bai ethnicity, respectively, p-trend<0.0001).

**Table 3** The prevalence of hyperuricaemia* and association of GGT level and hyperuricaemia in the participants among different age groups or gender groups

| GGT | Prevalence | | OR (95% CI) | P value | P for trend |
|---|---|---|---|---|---|
| **Age** | | | | | |
| **<45 years** | | | | | |
| Q1 | 46 (3.5) | $X^2$=435.7 | Reference | | <0.0001 |
| Q2 | 97 (7.6) | P<0.0001 | 1.51 (1.04 to 2.21)† | 0.03 | |
| Q3 | 117 (13.7) | | 2.23 (1.52 to 3.26) | <0.0001 | |
| Q4 | 145 (20.0) | | 2.41 (1.63 to 3.58) | <0.0001 | |
| Q5 | 256 (33.4) | | 3.32 (2.21 to 5.00) | <0.0001 | |
| **45–59 years** | | | | | |
| Q1 | 93 (4.9) | $X^2$=620.6 | Reference | | <0.0001 |
| Q2 | 176 (7.8) | P<0.0001 | 1.28 (0.97 to 1.68) | 0.09 | |
| Q3 | 281 (12.3) | | 1.60 (1.23 to 2.09) | 0.001 | |
| Q5 | 430 (18.3) | | 2.11 (1.62 to 2.74) | <0.0001 | |
| Q5 | 678 (28.4) | | 3.06 (2.33 to 4.01) | <0.0001 | |
| **>59 years** | | | | | |
| Q1 | 68 (10.1) | $X^2$=219.9 | Reference | | <0.0001 |
| Q2 | 136 (11.4) | P<0.0001 | 0.96 (0.69 to 1.36) | 0.81 | |
| Q3 | 230 (17.2) | | 1.35 (0.98 to 1.86) | 0.07 | |
| Q4 | 303 (21.7) | | 1.54 (1.12 to 2.16) | 0.008 | |
| Q5 | 417 (31.7) | | 2.42 (1.75 to 3.36) | <0.0001 | |
| **Gender** | | | | | |
| **Males** | | | | | |
| Q1 | 38 (11.9) | $X^2$=368.6 | Reference | | <0.001 |
| Q2 | 133 (13.1) | P<0.0001 | 1.01 (0.67 to 1.53) | 0.96 | |
| Q3 | 274 (17.8) | | 1.23 (0.83 to 1.82) | 0.31 | |
| Q4 | 499 (25.0) | | 1.58 (1.08 to 2.34) | 0.02 | |
| Q5 | 914 (38.4) | | 2.65 (1.79 to 3.91) | <0.0001 | |
| **Females** | | | | | |
| Q1 | 169 (4.7) | $X^2$=451.2 | Reference | | <0.0001 |
| Q2 | 276 (7.5) | P<0.0001 | 1.24 (1.00 to 1.54) | 0.05 | |
| Q3 | 354 (12.0) | | 1.72 (1.40 to 2.12) | <0.0001 | |
| Q4 | 379 (15.3) | | 2.03 (1.64 to 2.52) | <0.0001 | |
| Q5 | 437 (20.9) | | 2.62 (2.09 to 3.28) | <0.0001 | |

*Hyperuricaemia was defined as serum uric acid above 7.0 mg/dL for males and above 6.0 mg/dL for females.
†Fully adjusted model: adjusted for age (as appropriate), sex (as appropriate), BMI, ethnicity, education, smoking status, drinking habit, hypertension, hyperglycaemic, TG, LDL-c, HDL-c, serum creatinine and daytime napping duration, therapy for hypertension or other cardiovascular diseases, ALT, AST.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides.

hyperuricaemia was also defined as SUA above 5.6 mg/dL, so we conducted sensitivity analysis. The prevalence of hyperuricaemia and association of GGT level and hyperuricaemia were displayed in online supplemental table 1. The prevalence of hyperuricaemia with different serum GGT levels was 10.6%, 19.8%, 31.0%, 41.1% and 53.8%, respectively (p<0.0001). In the fully adjusted model, compared with the lowest quintile, the second, third, fourth and fifth quintiles of serum GGT exhibited a positive association with hyperuricaemia risk (OR=1.32, 1.68, 2.03 and 2.76, 95% CI=1.15 to 1.52, 1.46 to 1.93, 1.76 to 2.34 and 2.38 to 3.21, respectively, p-trend<0.0001). Logistic regression model was conducted separately in age, gender groups (online supplemental table 2). For all age groups, higher GGT levels were related to higher risk of hyperuricaemia (OR (95% CI): 2.88 (2.08 to 3.99)

**Table 4** The prevalence of hyperuricaemia* and association of GGT level and hyperuricaemia in the participants among different ethnic groups

| GGT | Prevalence | | OR (95% CI) | P value | P for trend |
|---|---|---|---|---|---|
| Ethnic group | | | | | |
| Han ethnicity | | | | | <0.0001 |
| Q1 | 131 (7.3) | $X^2$=665.4 | Reference | | |
| Q2 | 255 (11.8) | P<0.0001 | 1.26 (0.99 to 1.59)† | 0.06 | |
| Q3 | 390 (18.2) | | 1.63 (1.29 to 2.05) | <0.0001 | |
| Q4 | 504 (25.5) | | 1.99 (1.58 to 2.51) | <0.0001 | |
| Q5 | 724 (36.8) | | 2.89 (2.26 to 3.68) | <0.0001 | |
| Yi ethnicity | | | | | <0.0001 |
| Q1 | 46 (4.6) | $X^2$=346.4 | Reference | | |
| Q2 | 81 (6.4) | P<0.0001 | 1.02 (0.69 to 1.52) | 0.92 | |
| Q3 | 132 (11.3) | | 1.56 (1.07 to 2.27) | 0.02 | |
| Q5 | 203 (16.4) | | 1.81 (1.25 to 2.62) | 0.002 | |
| Q5 | 362 (27.3) | | 2.81 (1.93 to 4.11) | <0.0001 | |
| Bai ethnicity | | | | | <0.0001 |
| Q1 | 30 (2.8) | $X^2$=288.4 | Reference | | |
| Q2 | 73 (5.7) | P<0.0001 | 1.60 (0.99 to 2.58) | 0.05 | |
| Q3 | 106 (9.0) | | 1.82 (1.14 to 2.89) | 0.01 | |
| Q4 | 171 (13.5) | | 2.19 (1.39 to 3.46) | 0.001 | |
| Q5 | 265 (22.6) | | 3.04 (1.91 to 4.84) | <0.0001 | |

*Hyperuricaemia was defined as serum uric acid above 7.0 mg/dL for males and above 6.0 mg/dL for females.
†Adjusted for age, sex, BMI, education, smoking status, drinking habit, hypertension, hyperglycaemic, TG, LDL-c, HDL-c, serum creatinine, and daytime napping duration, therapy for hypertension or other cardiovascular diseases, ALT, AST.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglycerides.

for age<45 years group; 2.67 (2.14 to 3.33) for 45–59 years group; 2.57 (1.94 to 3.36) for age>59 years group; p-trend<0.0001). The highest levels of GGT were associated with higher risk of hyperuricaemia for males (OR (95% CI): 2.83 (2.13 to 3.74), p-trend<0.0001) and females (OR (95% CI): 2.41 (2.00 to 2.90), p-trend<0.0001). online supplemental table 3 displayed the association of GGT level and hyperuricaemia among different ethnic groups. Compared with first quintile, the highest GGT levels were related to higher risk of hyperuricaemia in three ethnic groups (OR (95% CI): 2.91 (2.37 to 3.59), 2.15 (1.16 to 2.86) and 2.74 (1.92 to 3.91) for Han, Yi and Bai ethnicity, respectively, p-trend <0.0001).

## DISCUSSION

hyperuricaemia is closely related to many metabolic diseases, and early prevention and treatment are very necessary. In the present study, we found that high serum GGT level increased the risk of hyperuricaemia in Chinese general population. After further adjusting for the confounding variables, there was still a strong positive association between serum GGT and hyperuricaemia. Also, there were associations between GGT and hyperuricaemia in different age groups, gender and ethnic groups. To the best of our knowledge, this is the first study to explore the association between GGT and risk of hyperuricaemia in less-developed ethnic minority regions in China. Our findings may provide new insights into the potential role of serum GGT in risk of hyperuricaemia.

As hypothesised, higher GGT levels were observed to have adverse effects on the risk of hyperuricaemia in Chinese general population. Our findings are consistent with those from previous literature. An analysis of 2486 middle-aged and elderly females found an elevated risk of hyperuricaemia with increasing GGT level after corrections for several covariates, which shared views similar to our results.[5] Jun-Xia Zhang et al enrolled 407 normotensive Chinese subjects, and they verified the relationship between GGT and hyperuricaemia in their observational study. They discovered that serum GGT was strongly related to the elevated uric acid level in normotensive Chinese adults. But some studies did not observe any associations. The discrepancies could explain by different races, sample size or adjusting different confounding variables.

In our study, the prevalence of hyperuricaemia is 15.8%, which was relatively higher than studies in Italian population reporting hyperuricaemia was 6.3% in healthy

subjects,[21] and 7.3% in hypertensive subjects.[22] The prevalences of hyperuricaemia were 13.7%–18.8% in different regions in China,[23] this might be attributed to different economic status and medical conditions. Subjects in our study were from less-developed ethnic minority regions and higher prevalence of hyperuricaemia might be due to less attention on physical examination, prevention and treatment. This is also supported by another study in Yunnan that the overall hyperuricaemia prevalence was 24.8% in Bai ethnicity.[24] Our participants were from Yunnan Province which is located in plateau where the prevalence of hypertension or prehypertension very high. Hypertension or antihypertensive drugs such as diuretic could influence the level of uric acid[25 26] and a study conducted in East European hypertensive participants indicating the prevalence was 25%.[27] These varying prevalence rates suggest that hyperuricaemia may be linked to geographical and ethnic factors. Also, we have adjusted hypertension treatment or other CVDs therapies, and the positive associations between GGT and hyperuricaemia remained.

Compared with previous literature, we conducted a separate analysis by ethnic groups. The positive relationship between GGT and hyperuricaemia was observed in three ethnic groups, including Han, Yi and Bai ethnicity. Some previous research has indicated the link between GGT and ethnicity. Ethnicity variation might link between GGT level and cardiometabolic diseases by influencing susceptibility to oxidative stress.[28–30] And the pro-oxidative effect of GGT had deleterious effects on the formation of renal vascular plaque and increased hyperuricaemia risk.[31 32] The prevalence of hyperuricaemia is 24.8% and 13.5% in Bai[24] and Yi ethnicity,[33] respectively. We conducted a separate analysis by age and gender. Higher level of GGT was related to higher risk of hyperuricaemia in different age or gender groups. This is consistent with previous studies. Both theirs and our results demonstrated that higher GGT level was related to a higher risk of hyperuricaemia in females. In our study, our analysis also indicated that the risk of hyperuricaemia in males increased after we adjusted for several potential confounding variables. In addition, our results showed that in Yunnan, one-sixth of people aged 30–79 had hyperuricaemia, and there is a male predominance in prevalence. Physiological differences and hormonal influences may explain the gender difference.

Despite the potential mechanism underlying the relationship between GGT and hyperuricaemia is not clear, there are some possible explanations. This might be interpreted as follows. First, the potential pro-oxidative effect of GGT.[31 32] The serum GGT level might parallel the level of SUA due to their relationship with oxidative stress in Chinese females. Second, insulin sensitivity may play a critical role in this relation. Serum GGT level was correlated with decreased insulin sensitivity, and the results were observed in healthy adults,[34] metabolic syndrome patients[34] and non-diabetes subjects.[35] GGT could predict the development of insulin resistance for healthy subjects.[11] While decreased insulin sensitivity may cause a reduction of urate excretion and increase in uric acid by stimulating renal tubular sodium-hydrogen exchange.[36 37] Third, increased SUA might be due to obesity related to GGT activities and lead to increased expression or decreased breakdown of SUA.[15] Compared with normal subjects, obese subject showed different levels of GGT.[38] Moreover, obesity also plays an vital role in elevating SUA level. Fourth, hepatocyte injury releases GGT as well as disrupting insulin signalling transduction and insulin resistance could cause an elevation of purine metabolism by activating of the hexose monophosphate shunt.[39] In turn, elevation of SUA could increase the risk of fatty liver disease and induce GGT secretion.

There were some strengths and limitations for the study. To the best of our knowledge, this is the first epidemiological study to investigate the association between GGT and hyperuricaemia risk in less-developed ethnic minority regions. Also, taking the effect of age, sex and ethnicity on the association between GGT and hyperuricaemia into consideration, we analysed the data stratifying by age, gender and ethnicity. Some limitations should also be considered. First, this is a cross-sectional study, a longitudinal study design is needed to explore temporal nature between GGT and hyperuricaemia. Second, we did not consider dietary habits as confounding variables, as some foods influence both GGT and uric acid level.[40–42] However, there is evidence that these foods are likely to have a smaller influence on both GGT and uric acid levels than alcohol.[40–43] We have adjusted the alcohol consumption in our model to minimise the bias. Third, the conclusion was limited to Chinese population and the generalisability to other races need to further explore. Finally, further studies need to be underlying to clarify the mechanisms.

## CONCLUSIONS

In the present study, we found that high serum GGT level was positively related to the risk of hyperuricaemia in less-developed ethnic minority regions in China. People who have higher level of GGT could pay close attention to their uric acid concentration.

**Ethics approval** The study met the standards for the ethical treatment of participants and was approved by Kunming Medical University Medical Ethical Review Board (KMMU2020MEC078).

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**Data availability statement** Data are available upon reasonable request.

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