Association between metabolic obesity phenotype, transition of metabolic phenotypes and the risk of hyperuricemia in Chinese adults
A cohort study

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Abstract
Prospective evidence on the association of obesity and metabolic health status and its transition over time with the risk of hyperuricemia in the Chinese population is limited. This study aims to investigate the phenotypic transition characteristics of metabolic obesity in Chinese adults and its association with hyperuricemia. Using the China Health and Retirement Longitudinal Survey (CHARLS) survey data in 2011 and 2015, 6059 adults aged ≥ 18 years were selected as the research people. The participants’ general information, living habits, blood sample testing, and blood uric acid testing data during follow-up were extracted. According to body weight and metabolic health status, obesity phenotypes were divided into: metabolically normal weight group (MHNW), metabolically normal overweight/obesity group (MHOWO); metabolically abnormal normal weight group (MUNW); metabolically abnormal overweight/obese group (MUHOWO). Multiple linear regression was used to evaluate the correlation between metabolic obesity phenotype and serum uric acid level, and logistic regression model was used to analyze the association of metabolic obesity phenotype and transition with the risk of hyperuricemia. The average age of all subjects was (58.62 ± 8.93) years old, and 42.1% were male. The MHOWO phenotype was present in 19.2% of the general population and 48.6% of the baseline who were overweight or obese population. During the 4-year follow-up period, only 10.7% of participants with MHNW at baseline converted to MHOWO. Among MHOWO participants, 21.2% converted to MUHOWO. MHOWO also increased the risk of hyperuricemia (OR, 1.57; 95% CI 1.15–2.13; P = .004), both in obese and normal-weight individuals, even when metabolic status changed from unhealthy to healthy. Risk of hyperuricemia was high among those who remained metabolically unhealthy but of normal weight (OR, 3.09; 95% CI 1.51–6.30; P = .001). MHOWO also increases the risk of hyperuricemia, and MHOWO remains stable or changes to MUHOWO, which increases the risk of hyperuricemia. Therefore, close attention should be paid to the transition of metabolic health status over time, and individualized prevention strategies should be focused on metabolically unhealthy and obese individuals.

Abbreviations: BMI = body mass index, CHARLS = China Health and Retirement Longitudinal Survey, MHNW = metabolically normal weight group, MHOWO = metabolically normal overweight/obesity group, MUHOWO = metabolically abnormal overweight/obese group, MUNW = metabolically abnormal normal weight group.

Keywords: hyperuricemia, metabolism, obesity, risk factors

1. Introduction
Hyperuricemia is a metabolic disease characterized by abnormally elevated blood uric acid levels. It not only directly leads to gout and impaired renal function, but is also closely related to various chronic diseases such as diabetes, hypertension, and cardiovascular and cerebrovascular diseases. In 2010, the prevalence of hyperuricemia among Chinese adults was 8.4%.[1] In 2015, a survey of adults aged 18-59 years in 15 provinces across the country found that the prevalence of hyperuricemia was 9.8%.[2] The “Guidelines for Diagnosis and Treatment of Hyperuricemia and Gout in China (2019 Edition)” stated that the prevalence of hyperuricemia in China has reached 13.3%.[3] Hyperuricemia has posed a serious threat to the health of Chinese residents.

Obesity and its associated metabolic disorders are major risk factors for hyperuricemia globally. However, there are differences in metabolic factors among obese patients, and some obese patients do not develop metabolic disorders and are defined as metabolically healthy obesity (MHOWO), but whether MHOWO is a healthy state is still controversial.[4,5] However, the MHOWO phenotype is not a stable state,[6] and studies have shown that 33% to 52% of MHOWO patients will transform into a metabolically unhealthy phenotype.[7,8]
However, there is no evidence on how MHOWO transitions in the Chinese population and its association with the risk of hyperuricemia. It remains unclear how metabolic factors change over time and how such dynamic metabolic transitions affect hyperuricemia risk among Chinese adults. Studies assessing the hyperuricemia hazards of dynamic metabolic transitions over time in China are of great both public health and clinical significance and provide strategies for early intervention.

In this study, the data from the China Health and Retirement Survey (CHARLS), a nationwide prospective cohort study, were used to analyze the change of metabolic obesity phenotype during the follow-up period and its association with the risk of hyperuricemia, so as to provide a scientific basis for the intervention and prevention of related high-risk populations.

2. Materials and methods

2.1. Data sources

This study used data from the China Health and Retirement Longitudinal Study (CHARLS), a longitudinal, nationally representative study of middle-aged and elderly residents (=45 years old) in China. The research survey draws samples according to a multi-stage regional probability sampling design, and constructs a high-quality public database containing extensive Chinese population data. The database contains detailed information on socioeconomic and demographic factors, household information, and health status. The original sample consisted of 17,708 respondents randomly selected from 450 villages/neighboring committees in 150 counties/districts in 28 provinces in 2011. Face-to-face computer-assisted personal interviews were conducted with respondents every 2 years. The CHARLS study was approved by the Biomedical Ethics Committee of Peking University (IRB00001052-11015), and all subjects participating in the study signed the informed consent.

This study selected 2011 as the baseline and 6059 adult residents with complete blood uric acid measurement data and demographic data in 2 follow-up surveys in 2015.

2.2. Selection of research subjects

The inclusion criteria are: Those who participated in 2 surveys in 2011 and 2015 at the same time; Complete blood test and physical examination data.

The exclusion criteria were: Patients with hyperuricemia at baseline examination; Missing key variables such as height, weight, blood pressure, and blood sugar.

2.3. Research methods

(1) Extract relevant information (age, gender, education level, marital status), living habits (current smoking status, drinking status), body mass index (BMI), hypertension, blood lipid profile, serum uric acid from the CHARLS database value. Four subgroups were divided according to the metabolic obesity phenotype.

(2) Relevant definitions

① Hyperuricemia: According to the definition of “Chinese Guidelines for Diagnosis and Treatment of Hyperuricemia and Gout (2019 Edition),” hyperuricemia is determined when serum uric acid exceeds 420 μmol/L (7.0 mg/dL).

② Obesity: According to the recommendations of the China Obesity Working Group, a BMI value ≥24 kg/m² is considered overweight; a BMI ≥ 28 kg/m² is considered obese.

③ Metabolic syndrome: According to the “Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 Edition),” those with or exceeding the following 3 components are defined as metabolic syndrome.

a. Abdominal obesity: female waist circumference ≥ 85 cm, male waist circumference ≥ 90 cm;

b. Hyperglycemia: fasting blood glucose ≥ 6.1 mmol/L or 2 hours post-glucose load blood glucose ≥ 7.8 mmol/L and (or) those who have been diagnosed with diabetes and treated;

c. Hypertension: blood pressure ≥ 130/85 mm Hg and (or) confirmed hypertension and treatment;

d. Fasting triglyceride ≥ 1.70 mmol/L;

e. Fasting HDL-C < 1.04 mmol/L.

(4) Obesity phenotype: According to the weight status grouping and metabolic syndrome components, the research subjects were defined as 4 types of obesity phenotypes: metabolically healthy normal weight group (MHNW); metabolically normal overweight/obesity group (metabolically healthy overweight/obesity, MHOWO); metabolically unhealthy normal weight (MUNW); metabolically unhealthy overweight/obesity (MUHWO) group.

2.4. Statistical methods

Continuous variables were expressed as mean ± standard deviation (x̄ ± s), and categorical variables were expressed as frequencies and percentages (n, %). When the data of different groups obeyed the normal distribution and the variance was homogeneous, analysis of variance was used, and the chi-square test was used to compare the classification data of different groups. Multiple linear regression was used to evaluate the correlation between metabolic obesity phenotype and serum uric acid level, and logistic regression model was used to analyze the association of metabolic obesity phenotype and transition with the risk of hyperuricemia. All data analyses were performed in SPSS 22.0 with α = 0.05.

3. Results

A total of 6059 participants were included in this study according to the selection criteria, including 2664 males (42.1%) and 3395 females (57.9%). According to metabolic health and obesity status, 1770 (30.0%) participants were metabolically unhealthy and 2499 (39.5%) participants were overweight or obese. The MHOWO phenotype was present in 19.2% of the general population (n = 1214) and in 48.6% of the overweight and obese population. It is worth noting that there were statistically significant differences in education level, smoking and drinking, blood pressure, blood lipid profile and other indicators among the groups (P < .05), as shown in Table 1.

The follow-up data in 2015 showed that the mean ± standard deviation of serum uric acid values between different phenotypes were, MHNW: 4.69 ± 1.31 mg/dL, MHOWO: 4.80 ± 1.27 mg/dL, MUNW: 5.06 ± 1.42 mg/dL, and MUHWO: 5.16 ± 1.30 mg/dL. Using the Bonferroni method for multiple correction, pairwise comparison found that the serum uric acid value in the MHNW group was lower than that in the MHOWO, MUNW, and MUHWO groups, and the difference was statistically significant (P < .05), as shown in Figure 1A. The mean ± standard deviation of serum uric acid values among the 4 phenotypic transitions in normal weight subjects were, respectively, MH to MH: 4.64 ± 1.28 mg/dL, MH to MU: 5.03 ± 1.33 mg/dL, MU to MU: 5.24 ± 1.41 mg/dL, MU to MH: 4.95 ± 1.39 mg/dL. The Bonferroni method was used for multiple correction, and it was found that the blood uric acid value of the MH to MH group was lower than that of the other 3 groups, and the difference was statistically significant (P < .05), as shown in Figure 1B. The mean ± standard deviation of serum uric acid values among the 4 phenotypic transitions in overweight and obese individuals...
were, respectively, MH to MH: 4.71 ± 1.23 mg/dL, MH to MU: 5.05 ± 1.30 mg/dL, MU to MU: 5.34 ± 1.45 mg/dL, MU to MH: 5.23 ± 1.27 mg/dL. Using the Bonferroni method for multiple corrections, it was found that the blood uric acid value of the MH to MH group was lower than that of the other 3 groups in pairwise comparison, and the difference was statistically significant (P < .05), as shown in Figure 1C. The 3 phenotypic transition groups, MH to MU, MU to MU, and MH to MU, had a higher prevalence of hyperuricemia than the metabolically stable (MH to MH) group in both normal-weight and obese subjects, see Figure 1D.

During the 4-year follow-up period, there were 370 new cases of hyperuricemia. MHOOWO individuals had a 57% increased risk of hyperuricemia compared with MHNW individuals (OR = 1.51–6.30, P < .01) was also higher than the risk of overweight and obese (OR = 2.02, 95%CI: 1.29–3.15, P < .01). For normal-weight subjects, the risk of hyperuricemia did not increase when transitioning from a metabolically healthy state to a metabolically unhealthy state (OR = 1.16, 95% CI: 0.78–3.34, P = .01). However, the risk of hyperuricemia was increased in overweight and obese individuals when they changed from a metabolically healthy state to a metabolically unhealthy state (OR = 2.09, 95%CI: 1.20–3.67, P = .01). Shifting from a metabolically unhealthy state to a healthy state in both normal-weight and overweight/obesity participants continued to increase the risk of hyperuricemia (see Table 4).

4. Discussion

This study is the first to identify the characteristics of metabolic obesity phenotype and its association with the risk of hyperuricemia in Chinese adults by using representative national population survey data. In Chinese adults, 21.2% of MHOOWO metabolic obesity phenotypes were converted to MUHOWO during the 4-year follow-up period. Stable unhealthy metabolic state and transition from metabolically healthy state to unhealthy state will increase the risk of hyperuricemia. The risk of developing hyperuricemia in a stable unhealthy metabolic state remains higher than in a transition from metabolically healthy obesity (MHOOWO) to unhealthy obesity (MUHOWO).

The results of this study suggest that individuals who remain metabolically unhealthy in a steady state have a higher risk of hyperuricemia than other categories of metabolically

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**Table 1**

| Variable (N%) | Normal weight | Overweight/Obesity |
|---------------|---------------|-------------------|
| N(%) | Metabolically healthy | Metabolically unhealthy | Metabolically healthy | Metabolically unhealthy | χ² | P |
| --- | --- | --- | --- | --- | --- | --- |
| Age | 59.33 ± 9.16 | 61.71 ± 9.07 | 55.74 ± 8.16 | 58.50 ± 8.33 | 70.13 | <.001 |
| Sex | Male 1583(51.5) | 189(39.0) | 414(34.1) | 478(37.2) | 147.20 | <.001 |
| Female 1492(48.5) | 296(61.0) | 800(65.9) | 807(62.8) | 147.20 | <.001 |
| BMI (kg/m²) | 20.99 ± 1.92 | 22.19 ± 1.49 | 26.56 ± 2.90 | 27.54 ± 2.68 | 3333.67 | <.001 |
| Education† | Middle school 2386(92.2) | 453(93.4) | 1085(89.4) | 1157(90.0) | 14.25 | .002 |
| High school 239(7.8) | 32(6.6) | 129(10.6) | 128(10.3) | 14.25 | .002 |
| Marital status | Married 2709(88.1) | 390(80.4) | 1125(92.7) | 1168(90.9) | 60.46 | <.001 |
| Non-married 366(11.9) | 95 (19.6) | 89(7.3) | 117 (9.1) | 130.80 | <.001 |
| Smoking status | Yes 1348(43.8) | 177(36.5) | 329(27.1) | 401(31.2) | 130.80 | <.001 |
| No 1727(56.2) | 308 (63.5) | 885(72.9) | 884 (68.8) | 77.65 | <.001 |
| Drinking status‡ | >1 866(28.2) | 390(80.4) | 250 (20.6) | 234(18.2) | 1285.00 | <.001 |
| <1 250(8.1) | 95 (19.0) | 96(7.9) | 90 (7.0) | 40.89 | <.001 |
| Waistline (cm) | 78.01 ± 9.24 | 84.93 ± 8.76 | 89.98 ± 9.56 | 95.45 ± 8.47 | 1285.00 | <.001 |
| Uric acid (mg/dL) | 4.17 ± 1.05 | 4.42 ± 1.11 | 4.18 ± 1.02 | 4.53 ± 1.05 | 40.89 | <.001 |
| Triglycerides(mg/dL) | 98.91 ± 52.68 | 212.09 ± 157.53 | 104.63 ± 42.73 | 225.91 ± 179.81 | 1746 | <.001 |
| Total cholesterol (mg/dL) | 188.54 ± 35.52 | 199.15 ± 41.77 | 193.78 ± 36.58 | 201.12 ± 42.48 | 38.42 | <.001 |
| LDL (mg/dL) | 113.75 ± 31.49 | 199.15 ± 41.77 | 123.02 ± 33.01 | 116.74 ± 38.87 | 23.86 | <.001 |
| HDL (mg/dL) | 56.86 ± 15.10 | 40.12 ± 12.65 | 32.27 ± 11.60 | 40.62 ± 11.74 | 547.26 | <.001 |
| SBP (mm Hg) | 124.40 ± 19.42 | 138.43 ± 21.25 | 127.44 ± 19.96 | 139.18 ± 20.14 | 205.09 | <.001 |
| DBP (mm Hg) | 72.20 ± 11.25 | 78.11 ± 9.24 | 75.88 ± 11.61 | 81.34 ± 11.58 | 200.77 | <.001 |

BMI = body mass index, DBP = diastolic blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, SBP = systolic blood pressure.

†Education level is divided into middle school and below, and high school and above.

‡The unit of drinking status is times/month.

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At present, the MHOWO phenotype is the most controversial among various metabolic obesity phenotype transitions and disease associations. Therefore, this study mainly analyzed the association between the MHOWO phenotype transition and the risk of hyperuricemia. Both normal-weight and overweight and obese participants had an increased risk of hyperuricemia compared with participants whose MH remained stable, even in normal-weight participants when metabolic status remained unhealthy, the risk of hyperuricemia (OR = 3.09, 95%CI: 1.51–6.30, P < .01) was also higher than the risk of overweight and obese (OR = 2.02, 95%CI: 1.29–3.15, P < .01). For normal-weight subjects, the risk of hyperuricemia did not increase when transitioning from a metabolically healthy state to a metabolically unhealthy state (OR = 1.16, 95% CI: 0.78–3.34, P = .20). However, the risk of hyperuricemia was increased in overweight and obese individuals when they changed from a metabolically healthy state to a metabolically unhealthy state (OR = 2.09, 95%CI: 1.20–3.67, P = .01). Shifting from a metabolically unhealthy state to a healthy state in both normal-weight and overweight/obesity participants continued to increase the risk of hyperuricemia (see Table 4).
obese phenotypic shifts. Metabolic phenotypic shifts in both MHOWO and MUHOWO individuals increase the risk of hyperuricemia. In recent years, several studies have reported the association of the metabolic obesity phenotype with hyperuricemia. A cross-sectional study reported that the mean serum uric acid level in the MHOWO group was 41.87 μmol/L higher than that in the MHNW group, and the mean increase in the MUHOWO group was 63.18 μmol/L.[11] A domestic study also came to a similar conclusion that hyperuricemia was positively correlated with the MHOWO, MUNW, and MUHOWO phenotypes, and this association was independent of gender and age.[12] The results of this study also found that the serum uric acid value and the prevalence of hyperuricemia in the MHOWO, MUNW, and MUHOWO groups were higher than those in the MHNW group. Studies have pointed out that this association also has gender differences. Through Bayesian network inference, the probability of hyperuricemia in MHOWO men is 0.076, while that in MHOWO women reaches 0.124.[13] However, there have been no reports of an association between metabolic obesity phenotypic shift and hyperuricemia. Previous domestic cohort studies on the association of metabolic obesity phenotype transition with cardiovascular disease also believed that for most Chinese adults, MHOWO is a transient state, stable metabolically unhealthy overweight or obese (MUHOWO) and metabolically unhealthy overweight or obese (MUHOWO). A transition from a healthy state to an unhealthy state is associated with a higher risk of developing observational disease than a stable healthy normal weight.[14] The largest study with the longest follow-up period that addressed the metabolic phenotype reported by Eckel et al found that obesity was still a risk factor for cardiovascular disease even if metabolic health was maintained for a long time. Meanwhile, a large proportion of women with healthy metabolism have changed into unhealthy phenotypes over time, which is related to the increased risk of

![Figure 1. Comparison of serum uric acid value and prevalence of hyperuricemia in different groups.](image)

![Figure 1. Comparison of serum uric acid value and prevalence of hyperuricemia in different groups.](image)

**Table 2**

Multivariate-adjusted associations of different obesity phenotypes with serum uric acid levels and hyperuricemia.

| Group   | Serum | UA | Hyperuricemia |
|---------|-------|----|---------------|
| MHOWO   | 0.013 | 0.45 0.16 8.10 | 1.57 (1.15, 2.13) | .004 |
| MUNW    | 0.086 | <0.001 0.95 0.18 27.67 2.58 (1.81, 3.67) | .001 |
| MUHOWO  | 0.095 | <0.001 0.89 0.14 43.41 2.45 (1.87, 3.19) | <.001 |

Adjusted variables are BMI, gender, age, education, marital status, smoking, and drinking.

MHAW = metabolically healthy normal weight, MHOWO = metabolically healthy overweight/obesity, MUNW = metabolically unhealthy normal weight, MUHOWO = metabolically unhealthy overweight/obesity.
Transitions of different metabolic obesity phenotypes from baseline to follow-up review.

| Metabolic obesity phenotype at baseline | MH to MH | MH to MU | MU to MH | MU to MU | Total |
|--------------------------------------|----------|----------|----------|----------|-------|
| MHNW                                 | 2534 (82.4) | 328 (10.7) | 137 (4.5) | 76 (2.5) | 3075 (100.0) |
| MHO                                  | 169 (13.9) | 774 (63.8) | 13 (1.0) | 258 (21.2) | 1214 (100.0) |
| MUNW                                 | 253 (82.2) | 60 (2.3) | 99 (20.4) | 73 (15.1) | 405 (100.0) |
| MUO                                  | 70 (5.4) | 480 (37.8) | 53 (4.1) | 678 (52.5) | 1285 (100.0) |
| Total                                | 3026 (49.9) | 1648 (27.2) | 302 (5.0) | 1083 (17.9) | 6059 (100.0) |

MH = metabolically healthy, MU = metabolically unhealthy.

Multivariate analysis of the association between different obesity phenotypes and the risk of hyperuricemia.

| Type                               | β  | SE   | Wald χ² | OR (95%CI) | P     |
|------------------------------------|----|------|---------|------------|-------|
| MH to MU                           | 0.47 | 0.37 | 1.59 | 1.16(0.78,3.34) | .208 |
| MH to MU                           | 1.16 | 0.36 | 10.14 | 3.09(1.51,6.30) | .001 |
| MU to MU                           | 0.87 | 0.27 | 10.34 | 2.31(1.36,3.92) | .001 |
| MU to MU                           | 0.75 | 0.29 | 6.92 | 2.12(1.21,3.27) | .009 |
| MU to MU                           | 0.71 | 0.23 | 9.71 | 2.03(1.30,3.17) | .002 |
| MU to MU                           | 0.50 | 0.25 | 3.90 | 1.65(1.00,2.70) | .048 |

MH = metabolically healthy, MU = metabolically unhealthy.

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Author contributions
Conception and design: Cheng Zhao. Administrative support: Cheng Zhao. Provision of study materials or patients: Cheng Zhao. Collection and assembly of data: Wenjing Zhao. Data analysis and interpretation: Wenjing Zhao. Manuscript writing: All authors. Final approval of manuscript: All authors.

Conceptualization: Cheng Zhao. Formal analysis: Wenjing Zhao. Investigation: Wenjing Zhao. Methodology: Cheng Zhao. Resources: Cheng Zhao. Software: Wenjing Zhao. Supervision: Cheng Zhao.
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