



Prevalence and risk factors associated with hyperuricemia among working population at high altitudes: a cross-sectional study in Western China

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Received: 26 July 2018 / Revised: 24 November 2018 / Accepted: 30 November 2018 / Published online: 3 January 2019
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Abstract

Chronic exposure to high altitude may lead to hyperuricemia. We investigated the prevalence of hyperuricemia and its risk factors among employees in high-altitude areas. A cross-sectional survey with cluster sampling was performed at 23 worksites on the Qinghai-Tibet Plateau. Subjects were evaluated by using questionnaires, anthropometric and laboratory measurements, and abdominal ultrasound. A multilevel logistic regression model and restricted cubic spline were used to explore the associated factors of hyperuricemia. Of the 4198 employees included in the study, the age-standardized prevalence of hyperuricemia was 28.1% (95% confidence interval (CI) 26.7–29.5), with 31.9% (95%CI 30.2–33.6) in men and 17.9% (95%CI 15.7–20.1) in women. Hypertension, hyperlipidemia, and a meat-food pattern were positively associated with hyperuricemia in both sexes, while diabetes, shift work, body mass index, non-alcoholic fatty liver disease, and low intake of fruits and vegetables were significantly associated with hyperuricemia only in men. Furthermore, a nonlinear dose-response association between the number of cardiovascular risk factors (CRFs) and hyperuricemia was observed. Compared with those having 0 CRFs, the full-adjusted odds ratios (ORs) and 95% CIs for 1, 2, and ≥ 3 CRFs were 1.76 (95%CI 1.25–2.47), 2.54 (95%CI 1.81–3.55), and 3.05 (95%CI 2.16–4.31) in men, respectively, and 2.13 (95%CI 1.43–3.17), 2.78 (95%CI 1.71–4.53), and 3.13 (95%CI 1.50–6.55) in women, respectively. Hyperuricemia is common in employees at high-altitude areas. However, working at higher altitudes does not mean necessarily higher risk of hyperuricemia, as dietary factors and clustered CRFs are more significant. Thus, workplace-based lifestyle modifications should be promoted.

Keywords Epidemiology · High altitude · Hyperuricemia · Prevalence · Risk factor · Worksite

Abbreviations

SUA	Serum uric acid
CRFs	Cardiovascular risk factors
BP	Blood pressure
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

TC	Total cholesterol
TG	Triglycerides
FBG	Fasting blood glucose
NAFLD	Non-alcoholic fatty liver disease
OR	Odds ratio
CI	Confidence interval

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Introduction

Hyperuricemia, defined as the presence of an elevated concentration of serum uric acid (SUA), is a strong predictor of the development of gout [1]. Moreover, hyperuricemia is not only related to the presence of hypertension, obesity, insulin resistance, and dyslipidemia [2, 3], but also increases the risks of stroke, heart disease, and chronic kidney disease. This has led to interest in hyperuricemia as a potentially modifiable cardiovascular risk factor [4].

Prevalence estimates for hyperuricemia based on population-based epidemiological surveys have been reported by a number of countries and regions, including western countries such as the USA, Italy, and Ireland, as well as the Asian countries such as Japan and South Korea [5–9]. Although the prevalence of hyperuricemia is seen to vary substantially worldwide, ranging from 11.4 to 29.5%, most are consistent with the increasing trend. Similarly, a nationwide survey conducted from 2007 to 2011 showed that 13.0% of adults in China had hyperuricemia, with the prevalence among men and women being 18.5% and 8.0%, respectively [10]. The country-to-country differences possibly reflect the differences in underlying genetic, environmental, and lifestyle factors. However, most relevant surveys were community-based and were conducted among a general population. Moreover, few have investigated the prevalence and risk factors of hyperuricemia in occupational populations, especially those working year-round at high altitudes.

High altitude is considered an altitude greater than 2400 m above sea level [11], and chronic exposure to high altitude has been linked to the generation of SUA [12]. A population study by Chen et al. found a high prevalence of hyperuricemia in Tibetans living at high altitudes: 31.1% of men and 18.2% of women [13]. The mechanism appears to involve the increased breakdown of adenine nucleotides and the effect of lactate to reduce uric acid excretion. There are many industry workers engaging in railway construction and electrical maintenance on the Qinghai-Tibet Plateau, and their health is vital for economic growth. Therefore, it is necessary to conduct studies on the prevalence and determinants of hyperuricemia to develop workplace wellness program. Moreover, previous investigations focused on the association of hyperuricemia with single cardiovascular risk factors (CRFs), such as hypertension and obesity, rather than with the clustering of multiple CRFs.

This study aims to estimate the current prevalence and risk factors of hyperuricemia among employees at high-altitude workplaces in Western China. The association between CRFs clustering and hyperuricemia is also evaluated.

Materials and methods

Study design and participants

A detailed description of the methods used in this study was published previously [14]. Briefly, a cross-sectional survey with cluster sampling was conducted between May 2013 and July 2013, to obtain a representative sample of the employees in the electric power industry in the Qinghai Province in Western China. First, the State Grid Corporation of China, a large state-owned monopoly enterprise guaranteeing electric power for the local residents, was chosen. It is composed of 23 geographically separate affiliates, which are the worksites

included in this study. Qinghai is located on the northeastern part of the Qinghai-Tibet Plateau, with an average altitude of 3000 m above sea level. The altitude distribution of the worksites in this study ranges from 2600 to 3700 m. Approximately 6000 full-time employees were in this enterprise at the time of the survey, and the general manager supported the investigation during working hours. All permanent employees aged 18 to 60 years who had been working for at least 2 years at the worksites were considered our subjects. Totally, 4975 employees were selected from all 23 worksites and invited to participate in this survey. Of the participants, 777 were excluded from the analysis for failing to complete either a questionnaire survey (248), a mandatory physical examination (156), or a laboratory measurement (373). Therefore, 4198 employees were included in the final analysis.

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the institutional review board at Peking University (IRB00001052-13023).

Data collection and anthropometry

Information on sociodemographic characteristics (age, sex, education, and occupation), lifestyle factors (smoking, alcohol consumption, fruit and vegetable intake, and preferred dietary pattern), and work-related factors (working altitude and work schedule) were collected using a self-administered questionnaire.

Measurements of height, weight, and blood pressure (BP) were conducted by trained health care professionals in a designated hospital. Weight was measured to an accuracy of 0.1 kg and height was measured to an accuracy of 0.1 cm. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). After at least 5 min of rest, three BP readings were made on the right arm with participants in a seated position using an automatic BP monitor device (Omron HEM-7201; Omron, Dalian, China) provided to all sites. This BP device has shown good accuracy for adults at high altitudes [15]. The mean of the latter two BP readings was used for all analyses.

Laboratory measurements and abdominal ultrasound

After an overnight fast of at least 8 h, the venous blood samples of subjects were obtained by trained physicians to test the levels of total cholesterol (TC), triglycerides (TG), serum uric acid (SUA), and fasting blood glucose (FBG) in a qualified laboratory, which has been operated under quality control by external assessments. Furthermore, abdominal ultrasound exams were performed by radiologists with more than 5 years of experience.

Definition of hyperuricemia and other factors

Hyperuricemia was defined as SUA levels ≥ 416 $\mu\text{mol/L}$ (7 mg/dl) in men and 357 $\mu\text{mol/L}$ (6 mg/dl) in women [16]. The major CRFs included hypertension, dyslipidemia, diabetes, overweight or obese, and current smoking [17]. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or undergoing current treatment with antihypertensive medications, according to the JNC-7 criteria [18]. Dyslipidemia was defined as an elevated TC (≥ 6.2 mmol/L) or TG (≥ 2.3 mmol/L), a self-reported previous diagnosis of dyslipidemia by a physician, or the taking of antidyslipidemic medications [19]. Diabetes was defined as a FBG ≥ 7.0 mmol/L or a self-reported physician-diagnosed diabetes [10]. The BMI criteria for overweight (24–27.9 kg/m²) and obese (≥ 28 kg/m²) were based on the Chinese guideline for obesity [20]. Current smoking was defined as the use of at least one cigarette per day, and frequent drinking was defined as consuming at least one drink per week, according to the previous study in China [21]. Low intake of fruits and vegetables was defined as self-reported low intake of fruits and vegetables. Participants were classified into three groups according to their preferred dietary pattern: vegetarian food, meat food, and mixed food—e.g., individuals who reported eating meat regularly were classified under the meat food dietary pattern. Moreover, participants were categorized into two groups based on their altitudes and work schedule (daytime/shift work). Non-alcoholic fatty liver disease (NAFLD) was diagnosed as fat accumulation without a history of excessive alcohol consumption, and the presence of a remarkably bright ultrasonic spectrum of liver in ultrasound images, including simple steatosis, fatty liver hepatitis, and cirrhosis [22].

Statistical analyses

Continuous variables are presented as mean \pm SD, except for TC and TG expressed as median (interquartile range) because of the skewed distribution. Categorical variables are presented as cases (*n*) and percentages (%). Comparisons between two groups were performed with *t* tests for normally distributed variables, *Wilcoxon rank-sum* tests for skewed distributed variables, and χ^2 tests for categorical data. The mean levels of SUA and prevalence of hyperuricemia were estimated for all participants and for different subgroups. Additionally, the age-standardized SUA levels and prevalence of hyperuricemia were calculated for overall population, based on the 2010 Chinese Census. One-way ANOVAs were used to compare the difference in mean SUA levels within subgroups, and Cochran-Armitage tests were used to assess trends in hyperuricemia prevalence within subgroups. To identify the risk factors of hyperuricemia, multilevel logistic regression models were built assuming worksite as a random effect, and covariates (age, education, job position, NAFLD,

working altitude, work schedule, smoking, drinking, low intake of fruits and vegetables, and preferred dietary pattern) were included as fixed effects in the models. To explore the dose-response relationship between the number of CRFs clustering as a continuous variable and the risk of hyperuricemia, a restricted cubic spline with three knots at fixed centiles (5%, 50%, and 95%) of the distribution was used and a test for the nonlinear association was calculated, coupled with the multi-level logistic regression models. All analyses were stratified by sex. All data analyses were conducted using SAS 9.4 (SAS institute, Cary, NC, USA) and a two-sided *p* value < 0.05 was considered statistically significant.

Results

Participant characteristics

The characteristics of overall participants are shown in Table 1. Of the 4180 subjects, 72.1% were men, 27.9% were women, and the mean age of participants was 40.5 ± 9.0 years. The majority (90.0%) were Han ethnic, and 76.4% had college or above education. Additionally, 89.3% were general staff, 92.8% were working at an altitude of 2600 to 3000 m, and 81.5% were daytime workers. The overall prevalence of NAFLD and hyperuricemia were 25.5% and 27.9%, respectively. Among men, 59.4% were current smokers, 13.8% were frequent drinkers, 16.4% had a low intake of fruits and vegetables, and 18.7% preferred the meat food pattern, as opposed to 3.2%, 0.9%, 5.6%, and 5.1% in women.

Distribution of SUA and prevalence of hyperuricemia

As shown in Table 2, the mean SUA level was 357.9 $\mu\text{mol/L}$ overall, with a mean level of 382.5 $\mu\text{mol/L}$ in men and 294.4 $\mu\text{mol/L}$ in women. The age-standardized level of SUA was 360.1 $\mu\text{mol/L}$ overall. The crude prevalence and age-standardized prevalence of hyperuricemia were 27.9% and 28.1%, respectively. Hyperuricemia was more common in men than in women, with the crude prevalence of 31.8% and 17.7%, and the age-standardized prevalence of 31.9% and 17.9%, respectively. The prevalence of hyperuricemia in men decreased with advancing age, whereas in women, it increased among those over 40 years old. The prevalence of hyperuricemia among participants whose education levels were high school or lower was similar to those whose education levels were college or higher, as was the case for supervisor versus general staff (*p* > 0.05). The prevalence of hyperuricemia increased with the BMI classification, and it was greater among participants with hypertension, NAFLD, and hyperlipidemia (all *p* < 0.001). However, the prevalence of hyperuricemia was lower among the diabetic men, while higher among the diabetic women. Geographically, the prevalence of

Table 1 Characteristics of the study participants

Characteristics	All (<i>n</i> = 4180)	Men (<i>n</i> = 3014)	Women (<i>n</i> = 1166)	<i>p</i> value
Age group (years), <i>n</i> (%)				< 0.001
20–29	789 (18.9)	615 (20.4)	174 (14.9)	
30–39	1002 (24.0)	703 (23.3)	299 (25.6)	
40–49	1879 (45.0)	1244 (41.3)	635 (54.5)	
50–60	510 (12.1)	452 (15.0)	58 (5.0)	
Age (years)	40.5 ± 9.0	40.5 ± 9.4	40.4 ± 7.7	0.889
Han ethnic, <i>n</i> (%)	3761 (90.0)	2725 (90.4)	1036 (88.9)	0.132
Education, <i>n</i> (%)				< 0.001
High school or below	988 (23.6)	774 (25.7)	214 (18.3)	
College or above	3192 (76.4)	2240 (74.3)	952 (81.7)	
Job position, <i>n</i> (%)				< 0.001
Supervisor	447 (10.7)	383 (12.7)	64 (5.5)	
General staff	3733 (89.3)	2631 (87.3)	1102 (94.5)	
SBP (mmHg)	117.4 ± 16.4	119.4 ± 16.5	112.2 ± 14.8	< 0.001
DBP (mmHg)	81.6 ± 10.9	83.1 ± 10.5	77.8 ± 11.0	< 0.001
BMI (kg/m ²)	23.3 ± 3.2	23.8 ± 3.1	21.9 ± 3.0	< 0.001
TC (mmol/L)	4.3 (3.8–4.9)	4.4 (3.9–5.0)	4.1 (3.6–4.7)	< 0.001
TG (mmol/L)	1.3 (0.9–2.0)	1.5 (1.0–2.2)	1.0 (0.8–1.5)	< 0.001
FBG (mmol/L)	5.0 ± 8.2	5.1 ± 7.8	5.0 ± 9.0	0.700
SUA (μmol/L)	357.9 ± 90.7	382.5 ± 84.9	294.4 ± 72.4	< 0.001
NAFLD, <i>n</i> (%)	1065 (25.5)	948 (31.5)	117 (10.0)	< 0.001
Hyperuricemia, <i>n</i> (%)	1165 (27.9)	959 (31.8)	206 (17.7)	< 0.001
Working altitude (m)				0.013
2600–3000	3880 (92.8)	2779 (92.2)	1101 (94.4)	
3000–3700	300 (7.2)	235 (7.8)	65 (5.6)	
Work schedule, <i>n</i> (%)				< 0.001
Daytime work	3408 (81.5)	2416 (80.2)	992 (85.1)	
Shift work	772 (18.5)	598 (19.8)	174 (14.9)	
Current smoking, <i>n</i> (%)	1827 (43.7)	1790 (59.4)	37 (3.2)	< 0.001
Frequent drinking, <i>n</i> (%)	427 (10.2)	417 (13.8)	10 (0.9)	< 0.001
Low intake of vegetable and fruit, <i>n</i> (%)	560 (13.4)	495 (16.4)	65 (5.6)	< 0.001
Meat food pattern, <i>n</i> (%)	622 (14.9)	563 (18.7)	59 (5.1)	< 0.001

Data are presented as number (%), mean ± SD or median (interquartile range). *p* value refer to comparisons between men and women

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; TG, triglycerides; FBG, fasting blood glucose; SUA, serum uric acid; NAFLD, non-alcoholic fatty liver disease

hyperuricemia was higher among participants who were working at altitudes of 3000 to 3700 m (32.0%), compared to those working at 2600 to 3000 m (27.6%), but the difference was not statistically significant ($p > 0.05$). The shift workers had a higher prevalence of hyperuricemia in men but not in women.

Factors affecting prevalence of hyperuricemia

The results of multilevel logistic regression analyses for hyperuricemia are showed in Table 3. In the full-adjusted model, hypertension, hyperlipidemia, and meat food pattern were positively associated with hyperuricemia in both

sexes. However, only in men, diabetes and shift work were negatively associated with hyperuricemia, while BMI, NAFLD, and low intake of fruits and vegetables were positively associated with hyperuricemia.

In addition, a nonlinear dose-response association between the number of CRFs clustering and hyperuricemia was observed in the initial analysis. The odds ratios (ORs) increased with the incremental numbers of CRFs clustering nonlinearly (p for nonlinearity < 0.001), with the largest association at the clustering of ≥ 3 CRFs (Fig. 1). Thus, the ORs of hyperuricemia were estimated by different numbers of CRFs clustering—i.e., 1, 2, and ≥ 3 —with the reference value of 0.

Table 2 Distribution of serum uric acid levels (μ mol/L) and prevalence of hyperuricemia by subgroups

	Serum uric acid levels, mean \pm SD			Prevalence of hyperuricemia, % (95%CI)		
	All	Men	Women	All	Men	Women
Crude	357.9 \pm 90.7	382.5 \pm 84.9	294.4 \pm 72.4	27.9 (26.5–29.2)	31.8 (30.2–33.5)	17.7 (15.6–20.0)
Age-standardized	360.1 \pm 90.1	383.2 \pm 84.0	294.7 \pm 71.8	28.1 (26.7–29.5)	31.9 (30.2–33.6)	17.9 (15.7–20.1)
Age group (years)						
20–29	365.6 \pm 87.3	387.3 \pm 78.3	289.3 \pm 72.8	29.4 (26.2–32.6)	33.3 (29.6–37.1)	15.5 (10.9–21.6)
30–39	355.7 \pm 91.2	384.4 \pm 83.8	288.2 \pm 69.5	26.6 (23.9–29.4)	32.3 (28.8–35.8)	13.4 (10.0–17.7)
40–49	352.7 \pm 91.2	381.2 \pm 86.1	296.9 \pm 73.2	27.5 (25.4–29.5)	31.7 (29.1–34.3)	19.2 (16.3–22.5)
50–60	369.4 \pm 91.2	376.5 \pm 91.0	314.3 \pm 71.3	29.4 (25.4–33.4)	29.4 (25.2–33.6)	29.3 (17.2–41.4)
<i>p</i> value	< 0.001	0.180	0.041	0.440	0.190	0.010
Education						
High school or below	355.9 \pm 91.9	372.3 \pm 88.8	296.5 \pm 77.2	26.1 (23.4–28.9)	28.3 (25.1–31.5)	18.2 (13.6–23.9)
College or above	358.5 \pm 90.3	386.0 \pm 83.2	293.9 \pm 71.3	28.4 (26.8–30.0)	33.0 (31.1–35.0)	17.5 (15.3–20.1)
<i>p</i> value	0.420	< 0.001	0.636	0.159	0.015	0.813
Job position						
Supervisor	375.2 \pm 74.9	388.1 \pm 66.6	298.0 \pm 74.6	27.9 (26.5–29.4)	32.4 (30.6–34.2)	26.6 (15.4–37.7)
General staff	355.8 \pm 92.2	381.7 \pm 87.2	294.2 \pm 72.3	27.5 (23.4–31.7)	27.7 (23.2–32.2)	17.2 (15.0–19.5)
<i>p</i> value	< 0.001	0.168	0.681	0.860	0.063	0.055
Hypertension						
Yes	376.7 \pm 96.6	387.1 \pm 95.9	324.1 \pm 82.1	34.9 (32.4–37.5)	35.0 (32.2–37.8)	34.4 (28.1–40.6)
No	349.0 \pm 86.2	379.7 \pm 77.4	287.4 \pm 68.0	24.5 (23.0–26.1)	29.9 (27.8–32.0)	13.7 (11.6–16.0)
<i>p</i> value	< 0.001	0.020	< 0.001	< 0.001	0.004	< 0.001
BMI group (kg/m ²)						
BMI < 24	340.0 \pm 88.0	368.5 \pm 82.5	288.7 \pm 72.9	22.0 (20.4–23.6)	25.0 (22.9–27.1)	16.6 (14.3–19.2)
24 \leq BMI < 28	381.6 \pm 85.5	394.1 \pm 83.1	314.7 \pm 64.7	35.0 (32.4–37.5)	37.6 (34.8–40.4)	21.0 (16.1–27.0)
BMI \geq 28	406.6 \pm 94.9	424.1 \pm 88.0	314.6 \pm 74.8	47.1 (41.2–53.0)	51.7 (45.2–58.2)	22.7 (12.8–37.0)
<i>p</i> value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.084
NAFLD						
Yes	392.7 \pm 94.1	401.8 \pm 92.0	319.1 \pm 76.8	39.4 (36.5–42.4)	41.2 (38.1–44.4)	24.8 (17.8–33.3)
No	346.0 \pm 86.3	373.6 \pm 79.9	291.7 \pm 71.4	23.9 (22.5–25.4)	27.5 (25.6–29.4)	16.9 (14.7–19.3)
<i>p</i> value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.033
Hyperlipidemia						
Yes	381.7 \pm 91.6	396.9 \pm 86.6	311.3 \pm 80.2	36.1 (34.1–38.2)	38.5 (36.2–40.8)	25.3 (20.8–29.7)
No	334.4 \pm 83.3	363.6 \pm 78.6	286.7 \pm 67.1	19.7 (18.1–21.5)	23.1 (20.9–25.4)	14.2 (11.9–16.8)
<i>p</i> value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Diabetes						
Yes	362.5 \pm 93.9	365.6 \pm 91.4	338.2 \pm 108.3	28.0 (26.6–29.4)	24.4 (19.0–30.7)	38.5 (18.4–58.5)
No	357.7 \pm 90.4	383.7 \pm 84.2	293.4 \pm 71.1	26.0 (20.3–31.7)	32.4 (30.6–34.1)	17.2 (15.1–19.5)
<i>p</i> value	0.431	0.003	0.002	0.508	0.018	0.005
Working altitude (m)						
2600–3000	357.1 \pm 90.7	381.5 \pm 85.6	295.7 \pm 72.2	27.6 (26.1–29)	31.3 (29.6–33.1)	18.0 (15.8–20.4)
3000–3700	368.1 \pm 89.5	394.3 \pm 74.8	273.1 \pm 72.5	32.0 (26.7–37.3)	37.4 (31.2–43.7)	12.3 (6.4–22.5)
<i>p</i> value	0.044	0.026	0.015	0.098	0.054	0.244
Work schedule						
Daytime work	358.2 \pm 90.5	384.5 \pm 83.8	294.2 \pm 72.4	28.6 (27.1–30.2)	33.1 (31.2–34.9)	17.8 (15.6–20.3)
Shift work	356.5 \pm 91.4	374.2 \pm 88.6	295.6 \pm 72.6	24.5 (21.6–27.6)	26.8 (23.2–30.3)	16.7 (11.9–22.9)
<i>p</i> value	0.630	0.008	0.813	0.020	0.003	0.708

The crude mean *SUA* within each subgroup was compared by one-way ANOVA and the crude prevalence rate was compared by χ^2 test or Cochran-Armitage test where appropriate

BMI, body mass index; *NAFLD*, non-alcoholic fatty liver disease

Stratified analyses were conducted for both men and women, and the results of multilevel logistic regression analyses are presented in Table 4. Compared with those having 0 CRFs, the full-adjusted ORs and their corresponding 95% confidence intervals (CIs) for men with 1, 2, and ≥ 3 CRFs were 1.76 (95%CI 1.25–2.47), 2.54 (95%CI 1.81–3.55), and 3.05 (95%CI 2.16–4.31), respectively, and the adjusted ORs (95%CIs) for women were 2.13 (95%CI 1.43–3.17), 2.78 (95%CI 1.71–4.53), and 3.13 (95%CI 1.50–6.55), respectively.

Discussion

Our study revealed a higher prevalence of hyperuricemia in an occupational sample at high altitudes. Multilevel logistic regression analyses showed that hypertension, hyperlipidemia, and meat food pattern were independent predictors of hyperuricemia in both sexes, whereas diabetes, shift work, BMI, NAFLD, and low intake of fruits and vegetables were all additionally associated with hyperuricemia in men. An equally important finding

Table 3 Risk factors associated with hyperuricemia in the multilevel logistic regression models

Characteristic	Men		Women	
	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
Fixed effects				
Age group (ref: 20–29, years)				
30–39	0.69 (0.53–0.89)	0.004	0.53 (0.30–0.96)	0.037
40–49	0.70 (0.54–0.90)	0.005	0.63 (0.37–1.10)	0.103
50–60	0.70 (0.51–0.97)	0.033	0.96 (0.42–2.21)	0.930
Education (ref: high school or below)				
College or above	1.14 (0.92–1.41)	0.232	1.39 (0.88–2.18)	0.154
Job position (ref: general staff)				
Supervisor	0.82 (0.62–1.08)	0.156	0.63 (0.32–1.23)	0.176
Hypertension (ref: no)				
Yes	1.21 (1.01–1.45)	0.045	1.93 (1.30–2.86)	0.001
BMI group (ref: BMI < 24, kg/m ²)				
24 ≤ BMI < 28	1.45 (1.20–1.74)	< 0.001	0.89 (0.58–1.37)	0.596
BMI ≥ 28	2.15 (1.57–2.95)	< 0.001	0.76 (0.33–1.74)	0.518
Hyperlipidemia (ref: no)				
Yes	1.86 (1.55–2.23)	< 0.001	1.91 (1.34–2.74)	< 0.001
Diabetes (ref: no)				
Yes	0.51 (0.36–0.73)	< 0.001	2.39 (0.97–5.91)	0.060
NAFLD (ref: no)				
Yes	1.58 (1.28–1.95)	< 0.001	1.50 (0.87–2.60)	0.144
Working altitude (ref: 2600–3000, m)				
3000–3700	1.19 (0.82–1.72)	0.353	0.86 (0.29–2.61)	0.794
Work schedule (ref: daytime work)				
Shift work	0.78 (0.63–0.97)	0.024	0.93 (0.57–1.51)	0.762
Current smoking (ref: no)				
Yes	0.95 (0.80–1.12)	0.527	1.66 (0.68–4.02)	0.263
Frequent drinking (ref: no)				
Yes	0.98 (0.78–1.24)	0.861	1.31 (0.29–5.84)	0.723
Low intake of vegetable and fruit (ref: no)				
Yes	1.40 (1.13–1.73)	0.002	1.01 (0.50–2.06)	0.981
Preferred dietary pattern (ref: vegetarian food)				
Meat food	1.37 (0.99–1.90)	0.053	1.64 (1.02–2.63)	0.040
Mixed food	1.23 (0.93–1.63)	0.142	1.41 (0.62–3.20)	0.410
Random effects				
Worksite-level variance (S.E)	0.29 (0.09)	< 0.001	0.65 (0.15)	< 0.001

Adjusted *ORs* with 95% *CI*s were reported from the multilevel logistic regression models with accounting intercept at worksites
OR, odds ratio; *CI*, confidence interval; *BMI*, body mass index; *NAFLD*, non-alcoholic fatty liver disease

was that the number of CRFs clustering increased the risk of hyperuricemia in terms of a nonlinear dose-response association.

The overall age-standardized prevalence of hyperuricemia was 28.1%, corresponding to 31.9% in men and 17.9% in women, which is similar to the prevalence of hyperuricemia in the Tibetan population at high-altitude areas [13], but higher than the prevalence of hyperuricemia in employees at sea level [23, 24]. Furthermore, the prevalence of hyperuricemia in the men of this study is higher than those in Japan (26.0%) [25]

and South Korea (23.1%) [26]. It should be noted that the sex-specific rate of hyperuricemia was considerably higher than in the Chinese general population (9.9% in men and 7.0% in women) [27], representing an emerging public health concern for the employees at high-altitude workplaces. Although the variations in prevalence rates can be mainly explained by the differences in ethnicities, regions, and demographic and lifestyle factors, chronic exposure to high-altitude environments may also be a contribution [12].

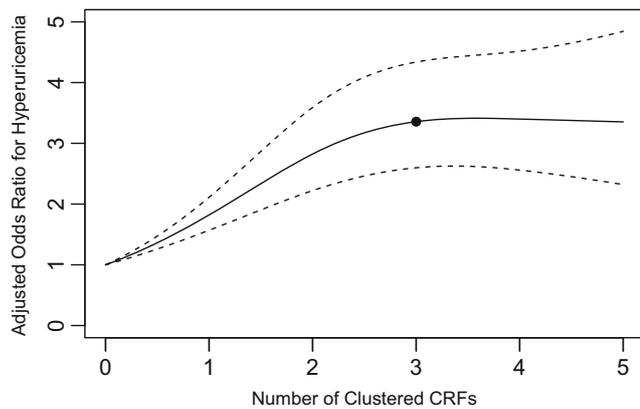


Fig. 1 Odds ratios for the association between the number of clustered CRFs (modeled as continuous variable) and presence of hyperuricemia. Dose-response model was adjusted for sex, age, education, job position, NAFLD, working altitude, work schedule, low intake of vegetable and fruit, and preferred dietary pattern. Dashed lines, 95% confidence interval. NAFLD, non-alcoholic fatty liver disease

Consistent with several epidemiological studies [3, 9, 28], we observed that the prevalence of hyperuricemia in men decreased gradually with age, while it increased in women aged 40 years or older, reaching a peak at 50 to 60 years. The sex-related differences in the correlation between age and hyperuricemia may be partially attributed to the interactions of sex hormones [3, 10]. The prevalence of hyperuricemia and SUA levels were higher in men than in women. Although differences in baseline characteristics—e.g., SBP, DBP, and BMI—between the sexes were probably major contributors, high androgen levels in young males could have also caused the difference by promoting kidney uric acid reabsorption [3].

A previous study conducted in China reported that education level was not associated with hyperuricemia [28], while another study showed higher education was positively associated with hyperuricemia [27]. In our study, there was no

significant association between hyperuricemia and education level. Moreover, the prevalence of hyperuricemia with regard to job position was not different. These findings may suggest that the process of urbanization and industrialization may narrow the gap regarding metabolic diseases between individuals with different socioeconomic characteristics.

NAFLD was identified as an important risk factor for hyperuricemia [24], and hyperuricemia may accelerate the development of NAFLD through a pro-inflammatory effect [29]. Although a consistent association between NAFLD and hyperuricemia was found in both sexes, a significant difference was only observed in men. The effect of shiftwork on hyperuricemia in men telecommunication workers has been reported in a longitudinal study, and it is thought that shiftwork might impact health by interfering with circadian rhythms [30]. However, we observed that shiftwork was a protective factor for hyperuricemia in men. According to Orth-Gomer [31], revised schedule of shift rotation from counterclockwise to clockwise may be better adapted to the autonomous circadian rhythms and produce a favorable effect on health. In addition, shift work is usually done by healthy workers, so we cannot exclude a healthy worker effect. Several studies have shown that hyperuricemia is increased in subjects living at high altitudes, and kidney damage and decreased excretion of SUA under hypoxic conditions could contribute to this pattern [11, 12]. However, we did not find differences in the prevalence of hyperuricemia between the two levels of altitude. The possible explanations are that long-term working and living at high altitudes result in a physiological adaptation to the environment [32], and altitude is not the major determinant of the presence of hyperuricemia. Other factors are more significant.

Hyperuricemia can be significantly influenced by dietary factors [27]. It is almost unanimous that beer and liquor can lead to a substantial increase of SUA, whereas moderate wine

Table 4 Clustered CRFs associated with hyperuricemia in the multilevel logistic regression models

Clustered CRFs	Men		Women	
	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
Fixed effects				
0	1.00 (ref)	–	1.00 (ref)	–
1	1.76 (1.25–2.47)	0.001	2.13 (1.43–3.17)	<0.001
2	2.54 (1.81–3.55)	<0.001	2.78 (1.71–4.53)	<0.001
≥3	3.05 (2.16–4.31)	<0.001	3.13 (1.50–6.55)	0.003
P for nonlinearity	<0.001		<0.001	
Random effects				
Worksite-level variance (S.E.)	0.31(0.09)	<0.001	0.61(0.14)	<0.001

Age, education, job position, NAFLD, working altitude, work schedule, frequent drinking, low intake of vegetable and fruit, and preferred dietary pattern were adjusted in the multilevel logistic regression models with accounting intercept at worksites, and adjusted ORs with 95% CIs were reported

OR, odds ratio; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease

drinking does not increase the risk [28]. We found no significant association between drinking and the prevalence of hyperuricemia, and inconsistent definitions for alcohol use could have caused the differences. Furthermore, high levels of purine-rich meat consumption are associated with an increased risk of hyperuricemia [33], while higher amounts of fruits and vegetables may decrease the risk [30]. As indicated in our study, meat food pattern is a significant risk factor of hyperuricemia in both sexes, while a low intake of fruits and vegetables increases the risk only in men.

The major CRFs have been known to have a relationship with the elevation of the SUA level [2, 10]. Our study confirmed that hypertension and hyperlipidemia are positively associated with hyperuricemia. In accordance with a Japanese study [34], we found that diabetes was negatively associated with hyperuricemia only in men, perhaps due to the inhibition of uric acid reabsorption in the proximal tubules by elevated glucose levels [35]. Moreover, high BMI, a proven risk factor for hyperuricemia, was found to be associated with hyperuricemia in men rather than in women. Therefore, the differences in physiologic impact, or in the severity of diabetes and obesity between sexes in our study, may be the major contributing factors to sex-specific effects.

Similar to an earlier finding in the general Chinese population [10], we found a dose-response association between the number of CRF clustering and hyperuricemia in the working population after adjusting for covariates—namely, a greater number of CRFs clustering was associated with a higher risk of hyperuricemia in both sexes. Additionally, we offered new insight by detailing that this relationship was nonlinear. Emerging evidence demonstrated that CRFs clustering has more adverse cardiovascular effects than that predicted by single risk factors [36], and a stronger association of hyperuricemia with clustered CRFs was observed in women than in men, which may explain the phenomenon of stronger association between hyperuricemia and cardiovascular event onset in women [37].

Limitation

This study has several limitations. First, this survey was conducted in a homogenous working population at high altitudes, which may not represent the employees in other regions, as the prevalence and components of the CRFs could be strongly influenced by age, sex, and ethnicity. Second, due to the nature of cross-sectional studies, the causal relationship between risk factors and hyperuricemia cannot be made, and SUA level was only evaluated once in this study, which may impact the estimates of the prevalence of hyperuricemia. Third, the dietary pattern of the Qinghai-Tibet Plateau characterized by purine-rich foods (e.g., beef and mutton offal and buttered tea) are important for the elevated SUA levels. However, the detailed diet

structure of the subjects could not be analyzed since that information was not specifically collected in this study. Fourth, several factors correlating to hyperuricemia were not assessed, including diuretic antihypertensive drugs [10], renal function [9], and physiologic parameters influenced by chronic exposure to high altitude, such as hematocrit [12]. Future study is needed to examine the physiologic parameters and to identify the underlying mechanisms of altitude's impact on SUA. Finally, we acknowledge that the limited information on alcohol consumption could be a possible reason for the lack of association with hyperuricemia observed in this study. However, despite these limitations, this was the first to analyze the prevalence of hyperuricemia and its risk factors in the working population at high-altitude regions in China. The multilevel models were also applied to determine the association of hyperuricemia with single risk factors, as well as with the CRFs clustering after controlling for the clustering effects at worksites.

Conclusions

In summary, although hyperuricemia is prevalent in the working population on the Qinghai-Tibet Plateau for the employees aged 20 to 60 years, there are no altitude-related differences regarding the risk of hyperuricemia. We found that some CRFs and dietary factors were independently associated with the risk of hyperuricemia, while sex-specific differences existed. Moreover, hyperuricemia was significantly associated with the coexistence of more CRFs, particularly in women. Therefore, workplace-based lifestyle intervention are urgently needed to prevent hyperuricemia and CRFs among the employees, and more studies are warranted to clarify the underlying mechanism of these relationships.

Acknowledgements We would like to acknowledge all the employees who participated in the study and investigators for their valuable help in data collection.

Author contribution CC and YW conceived and designed the study, YS analyzed the data and wrote the paper, CC reviewed and edited the paper, SL helped in preparing the database and helped in the data analysis, WL and BN edited the paper, and all authors read and approved the final manuscript.

Compliance with ethical standards

Disclosures None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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References

- Bardin T, Richette P (2014) Definition of hyperuricemia and gouty conditions. *Curr Opin Rheumatol* 26(2):186–191
- Nagahama K, Iseki K, Inoue T, Touma T, Ikemiya Y, Takishita S (2004) Hyperuricemia and cardiovascular risk factor clustering in a screened cohort in Okinawa, Japan. *Hypertens Res* 27(4):227–233
- Qiu L, Cheng XQ, Wu J, Liu JT, Xu T, Ding HT, Liu YH, Ge ZM, Wang YJ, Han HJ, Liu J, Zhu GJ (2013) Prevalence of hyperuricemia and its related risk factors in healthy adults from northern and northeastern Chinese provinces. *BMC Public Health* 13:664
- Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, Manolis AJ, Perez-Ruiz F, Mancia G (2015) Serum uric acid and the risk of cardiovascular and renal disease. *J Hypertens* 33(9):1729–1741
- Trifiro G, Morabito P, Cavagna L, Ferrajolo C, Pecchioli S, Simonetti M, Bianchini E, Medea G, Cricelli C, Caputi AP et al (2013) Epidemiology of gout and hyperuricaemia in Italy during the years 2005–2009: a nationwide population-based study. *Ann Rheum Dis* 72(5):694–700
- Zhu Y, Pandya BJ, Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 63(10):3136–3141
- Kumar AUA, Browne LD, Li X, Adeeb F, Perez-Ruiz F, Fraser AD, Stack AG (2018) Temporal trends in hyperuricaemia in the Irish health system from 2006–2014: a cohort study. *PLoS One* 13(5):e0198197
- Nagahama K, Inoue T, Kohagura K, Ishihara A, Kinjo K, Ohya Y (2014) Hyperuricemia predicts future metabolic syndrome: a 4-year follow-up study of a large screened cohort in Okinawa, Japan. *Hypertens Res* 37(3):232–238
- Kim Y, Kang J, Kim GT (2018) Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. *Clin Rheumatol* 37(9):2529–2538
- Wu J, Qiu L, Cheng XQ, Xu T, Wu W, Zeng XJ, Ye YC, Guo XZ, Cheng Q, Liu Q, Liu L, Xu CL, Zhu GJ (2017) Hyperuricemia and clustering of cardiovascular risk factors in the Chinese adult population. *Sci Rep* 7(1):5456
- Arestegui AH, Fuquay R, Sirota J, Swenson ER, Schoene RB, Jefferson JA, Chen W, Yu XQ, Kelly JP, Johnson RJ, Escudero E (2011) High altitude renal syndrome (HARS). *J Am Soc Nephrol* 22(11):1963–1968
- Jefferson JA, Escudero E, Hurtado ME, Kelly JP, Swenson ER, Wener MH, Burnier M, Maillard M, Schreiner GF, Schoene RB, Hurtado A, Johnson RJ (2002) Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. *Am J Kidney Dis* 39(6):1135–1142
- Chen W, Liu Q, Wang H, Chen W, Johnson RJ, Dong X, Li H, Ba S, Tan J, Luo N, Liu T, He H, Yu X (2011) Prevalence and risk factors of chronic kidney disease: a population study in the Tibetan population. *Nephrol Dial Transplant* 26(5):1592–1599
- Shen Y, Chang C, Zhang J, Jiang Y, Ni B, Wang Y (2017) Prevalence and risk factors associated with hypertension and prehypertension in a working population at high altitude in China: a cross-sectional study. *Environ Health Prev Med* 22(1):19
- Cho K, Tian M, Lan Y, Zhao X, Yan LL (2013) Validation of the Omron HEM-7201 upper arm blood pressure monitor, for self-measurement in a high-altitude environment, according to the European Society of Hypertension International Protocol revision 2010. *J Hum Hypertens* 27(8):487–491
- Fang J, Alderman MH (2000) Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. *JAMA* 283(18):2404–2410
- Yang ZJ, Liu J, Ge JP, Chen L, Zhao ZG, Yang WY, China National D (2012) Metabolic Disorders Study G: Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007–2008 China National Diabetes and Metabolic Disorders Study. *Eur Heart J* 33(2):213–220
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr et al (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289(19):2560–2572
- Hu DY, Ding RJ (2008) Guidelines for management of adult dyslipidemia in China. *Zhonghua Nei Ke Za Zhi* 47(9):723–724
- Zhou BF (2002) Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases—report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci* 15(3):245–252
- Wang Z, Hao G, Wang X, Wang W, Chen W, Zhu M (2016) Hypertension Control in Community Health Center Project G: Short-term hypertension management in community is associated with long-term risk of stroke and total death in China: a community controlled trial. *Medicine (Baltimore)* 95(48):e5245
- Sanyal AJ, American Gastroenterological A (2002) AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology* 123(5):1705–1725
- Chen X, Li Y, Sheng CS, Huang QF, Zheng Y, Wang JG (2010) Association of serum uric acid with aortic stiffness and pressure in a Chinese workplace setting. *Am J Hypertens* 23(4):387–392
- Cui L, Meng L, Wang G, Yuan X, Li Z, Mu R, Wu S (2017) Prevalence and risk factors of hyperuricemia: results of the Kailuan cohort study. *Mod Rheumatol* 27(6):1066–1071
- Sugie T, Imatou T, Miyazaki M, Une H (2005) The effect of alcoholic beverage type on hyperuricemia in Japanese male office workers. *J Epidemiol* 15(2):41–47
- Ryu S, Chang Y, Zhang Y, Kim SG, Cho J, Son HJ, Shin H, Guallar E (2012) A cohort study of hyperuricemia in middle-aged south Korean men. *Am J Epidemiol* 175(2):133–143
- Liu H, Zhang XM, Wang YL, Liu BC (2014) Prevalence of hyperuricemia among Chinese adults: a national cross-sectional survey using multistage, stratified sampling. *J Nephrol* 27(6):653–658
- Liu L, Lou S, Xu K, Meng Z, Zhang Q, Song K (2013) Relationship between lifestyle choices and hyperuricemia in Chinese men and women. *Clin Rheumatol* 32(2):233–239
- Gong S, Song J, Wang L, Zhang S, Wang Y (2016) Hyperuricemia and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 28(2):132–138
- Uetani M, Suwazono Y, Kobayashi E, Inaba T, Oishi M, Nogawa K (2006) A longitudinal study of the influence of shift work on serum uric acid levels in workers at a telecommunications company. *Occup Med (Lond)* 56(2):83–88
- Orth-Gomer K (1983) Intervention on coronary risk factors by adapting a shift work schedule to biologic rhythmicity. *Psychosom Med* 45(5):407–415
- Taino G, Giardini G, Pecchio O, Brevi M, Giorgi M, Verardo MG, Detragiache E, Imbriani M (2012) Work at high altitudes: risk factors and health surveillance. *G Ital Med Lav Ergon* 34(3 Suppl):235–237
- He F, Wang LL, Yu XL (2017) Dietary patterns associated hyperuricemia among Chinese aged 45 to 59 years: an observational study. *Medicine* 96(50):e9248

34. Oda E, Kawai R, Sukumaran V, Watanabe K (2009) Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men. *Intern Med* 48(20):1785–1791
35. Nan H, Dong Y, Gao W, Tuomilehto J, Qiao Q (2007) Diabetes associated with a low serum uric acid level in a general Chinese population. *Diabetes Res Clin Pract* 76(1):68–74
36. Zhang L, Qin LQ, Cui HY, Liu AP, Wang PY (2011) Prevalence of cardiovascular risk factors clustering among suburban residents in Beijing, China. *Int J Cardiol* 151(1):46–49
37. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W, Tang Z (2016) Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. *Sci Rep* 6:19520