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Sex differences in the associations between prior weight loss and all-cause or cardiovascular mortality in non-elderly individuals with hyperuricemia: a mortality follow-up study

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Abstract

Background Hyperuricemia, a common metabolic condition, is strongly associated with obesity and represents as an independent risk factor for elevated risk of mortality. This observational study aimed to examine the sex-specific associations of prior long-term weight loss (LTWL), defined as a sustained reduction in body weight maintained for at least 12 months, with all-cause and cardiovascular disease (CVD) mortality in non-elderly individuals with hyperuricemia.

Methods Non-elderly individuals with hyperuricemia and a historical maximum body mass index ≥ 25 kg/m^2 from the 1999–2018 US National Health and Nutrition Examination Survey were included. Sex-specific associations between prior LTWL (< 5%, 5-9.9%, 10-14.9%, and ≥ 15%) with all-cause and CVD mortality were investigated by weighted multivariable Cox proportional hazard regression analysis and stratified analysis.

Results Among 5,130 participants included, 505 all-cause (147 from CVD) deaths occurred during a median follow-up of 113 months. Compared with the LTWL < 5% reference group, the hazard ratios and 95% confidence intervals for the LTWL 5-9.9%, 10-14.9% and ≥ 15% groups were 1.11 (0.72–1.71), 1.34 (0.79–2.26) and 1.85 (1.14–2.92), respectively, for all-cause mortality (P for trend = 0.02) and 1.83 (0.76–4.43), 2.15 (0.76–6.10), and 3.76 (1.51–9.36), respectively, for CVD mortality (P for trend = 0.003). Significant associations between LTWL with all-cause and CVD mortality were observed exclusively in female, not male participants.

Conclusions Prior LTWL ≥ 5% was associated with increased all-cause and CVD mortality in US non-elderly female participants with hyperuricemia. Additional prospective and longitudinal randomized clinical trials are necessary to further examine the current findings.

Keywords All-cause mortality, Cardiovascular disease mortality, Hyperuricemia, Long-term weight loss, NHANES, Obesity, Overweight

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Introduction

Hyperuricemia, a prevalent condition stemming from aberrant uric acid metabolism, is observed globally, particularly in developed countries. Increasing evidence indicates that hyperuricemia and overweight/obesity are closely related and frequently co-occur clinically. A causal relationship between obesity and hyperuricemia has also been established in previous studies using Mendelian randomization [1]. Extensive research has consistently demonstrated a significant association between hyperuricemia and elevated risk of all-cause and cardiovascular disease (CVD) mortality [2]. Similarly, a recent meta-analysis further substantiated that urate-lowering therapy significantly reduce all-cause and CVD mortality in patients with hyperuricemia [3].

Although weight loss has been consistently demonstrated to improve cardiometabolic profiles [4], its impact on the risk of premature mortality remains largely unknown. An earlier meta-analysis of randomized clinical trials has suggested that modest weight loss, defined as a loss of 5–10% of the initial body weight, could significantly reduce the morbidity and mortality rate in obese patients [5]. However, several large population studies, including the Singapore Chinese Health Study, the National Health Insurance Program in Korea, and the ADDITION-Europe trial, have consistently indicated that weight loss is associated with an increased risk of all-cause and cause-specific mortality [6–8]. In a recent large-scale study involving 8,297 obese patients with established CVD followed for a median of 13.9 years, Zhang et al. found that a loss of over 5 kg of body weight was not associated with an increased risk of all-cause and CVD mortality [9]. The exact reasons for these conflicting results are unclear, and factors such as differences in participant demographics, underlying comorbidities, baseline weight status, and weight fluctuations have been suggested [10–12].

Another unresolved issue is the influence of sex, as emerging evidence highlights that the effect of weight loss on long-term mortality might differ between men and women. For instance, Tolvanen et al. demonstrated that a weight loss of over 10 kg in men was associated with 55% and 55% increased risk of all-cause and CVD mortality, respectively, which nonetheless was not observed in women [13]. In comparison, the Rancho Bernardo study concluded that weight loss was associated with an increased risk of all-cause and CVD mortality in older adults, regardless of sex [14].

To the best of our knowledge, the impact of prior weight loss on the mortality risk in individuals with current hyperuricemia, a vulnerable population already at increased risk of mortality, remains poorly understood. To address this research gap, the present study examined the associations between prior weight loss and all-cause or CVD mortality specifically among currently hyperuricemic patients. Additionally, we are also intrigued to examine whether participants' sex had a significant impact on this association. The findings of this study may provide physicians with practical guidance on the sex-specific management strategies for hyperuricemic adults with a history of weight loss.

Materials and methods

Study population

The data were derived from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional, biennial, nationally representative survey of the health and nutritional status of the non-institutionalized US population using a complex, stratified, multistage probability sampling design. Interviews, physical examinations, and measurements of biological samples were conducted and relevant data were collected. The NHANES protocol and procedures were approved by the Institutional Review Board of National Center for Health Statistics, and all adult participants provided informed consent.

The study included adult participants (≥ 20 years of age) from 10 waves of the NHANES 1999–2018 with hyperuricemia, defined as serum uric acid levels exceeding 7 mg/dL for men or 6 mg/dL for women, or those taking urate-lowering agents. Blood uric acid levels were measured using the Roche Cobas 6000 (c501 module). Participants were excluded from the final analysis based on the following criteria: (1) age > 64 years ($n = 3084$); (2) pregnancy at the time of interview ($n = 23$); (3) with a history of cancer ($n = 56$); (4) missing body weight ($n = 307$); (5) missing follow-up ($n = 12$); and (6) a self-reported historical maximum body mass index (BMI) < 25 kg/m^2 or a BMI < 18.5 kg/m^2 within the past year in case of the potential for an underlying medical condition ($n = 383$). The rationale for limiting the age range to 20–64 years is consistent with the guideline of the American Society for Nutrition and the North American Association for the Study of Obesity, which indicate that body weight stabilizes between the ages of 20 and 60 to 70 years [15]. The upper age limit of 64 years was chosen in accordance with previous reports and to homogenize our study population to young and middle-aged adults [16]. Finally, data from a total of 5,388 participants were available for analysis. The study flow chart is presented in Fig. 1.

Primary outcome

The primary outcomes were all-cause mortality and CVD mortality. All-cause mortality was defined as deaths from any cause, and CVD mortality was defined as participants with deaths attributable to CVD, as classified by the International Classification of Diseases, 10th Edition (ICD-10) codes I00-I09, I11, I13, and I20-I51, by linking

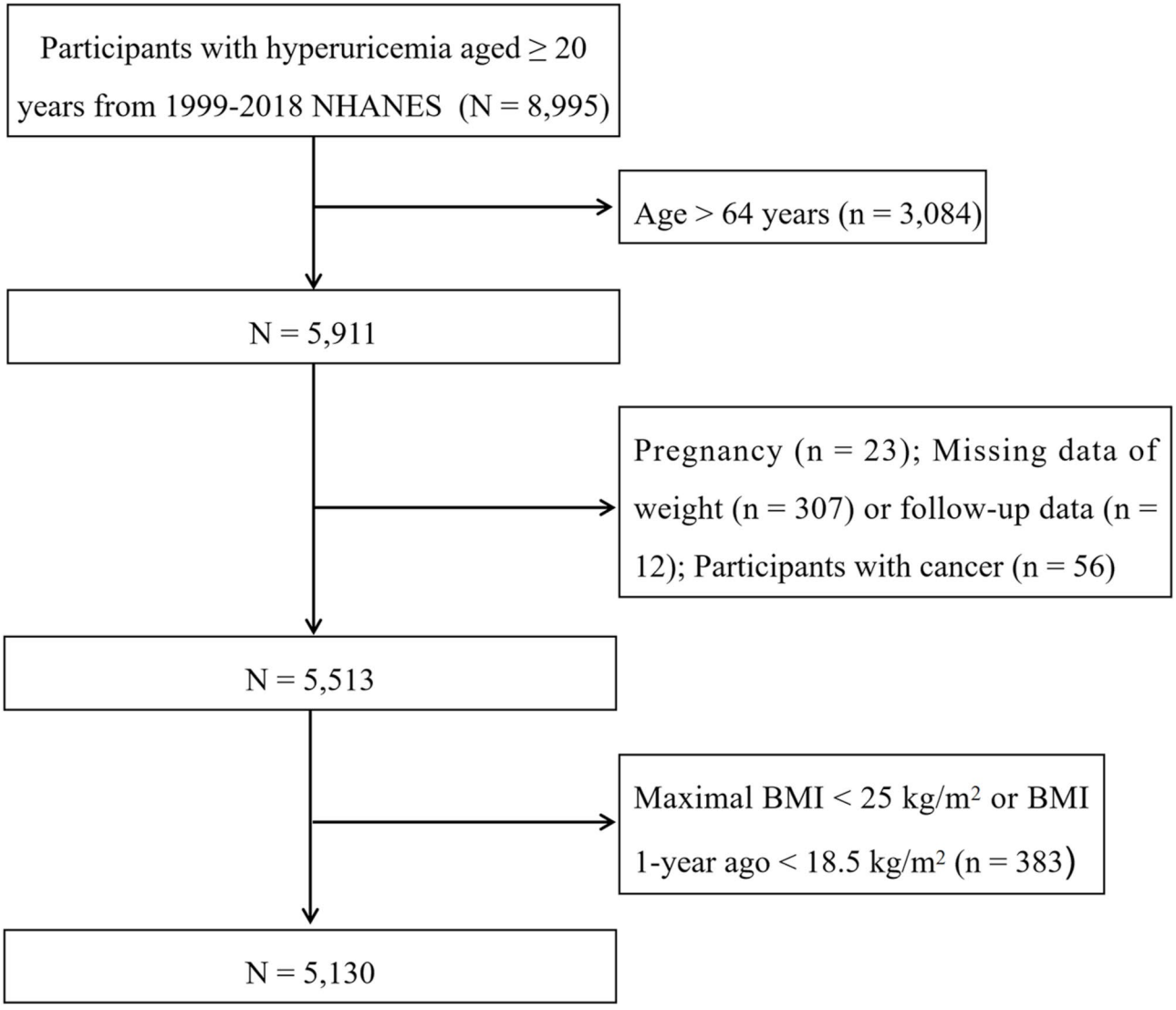

Fig. 1 Study flowchart. BMI, body mass index; NHANES, National Health and Nutrition Examination Survey

to the death records at the National Death Index up to December 31, 2019 [17].

Main exposure

The primary exposure was long-term weight loss (LTWL), defined as a sustained reduction in body weight maintained for at least 12 months. To calculate LTWL, data on historical maximum weight, weight from 1 year ago, and current weight, were all obtained by self-report in the NHANES "Weight History" module. The LTWL was calculated as [self-reported historical maximum weight - self-reported weight 1 year ago or current weight (the higher of the 2)]/self-reported historical maximum weight × 100% [18]. The rationale for using the higher values of the self-reported weight from 1 year ago and the current weight is to compliance with the requirement of weight reduction maintenance for at least one year. As an example, an individual with a historical maximum weight of 120 kg, a 1-year-ago weight of 100 kg, and a current weight of 115 kg would have a LTWL of (120 – 115) / 120 × 100% = 4.2%, rather than (120 – 100) / 120 × 100% = 16.67%. Based on previous empirical experience [19, 20], the LTWL was categorized into < 5% (reference, stable), 5-9.9% (moderate), 10-14.9% (severe), and 15% (extreme) groups.

Covariates assessment

Demographic and socioeconomic data, including age, sex, race/ethnicity, marital status, education level and poverty-income ratio, smoking status and alcohol consumption were all collected by questionnaires during the home interview. Smoking status was categorized into never, former, or current. The criteria for categorizing alcohol consumption into never, former, mild,

moderate and severe were consistent with those previously reported [21]. Information on comorbidities of hypertension, diabetes, and coronary heart disease was also collected. Diabetes was considered to be present in participants with a physician-confirmed medical history of diabetes, or a glycated hemoglobin A1C > 6.5%, or a fasting blood glucose > 7.0 mmol/L, or a 2-hour post-load oral glucose tolerance test ≥ 11.1 mmol/L, or current use of anti-diabetic medications [22]. Hypertension was diagnosed in participants with a self-reported history of hypertension, or a blood pressure ≥ 140/90 mmHg at the Mobile Examination Center or currently taking anti-hypertensive medications. Physical activity over the last 30 days was also collected from questionnaires. Waist circumference was measured at the uppermost lateral border of the right ilium. Participant's triglyceride, high-density lipoprotein cholesterol, total cholesterol and serum creatinine were all obtained from the standard laboratory tests. Data regarding the use of urate-lowering agents were also collected. Kidney function, as indicated by the estimated glomerular filtration rate, was assessed with the 2009 serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation [23].

Statistical analysis

In accordance with NHANES analytic guidelines, we applied appropriate weighting to obtain nationally representative estimates. Study participants were categorized based on LTWL for comparison of baseline characteristics. Continuous variables were presented as mean ± standard error and compared by weighted one-way analysis of variance. Categorical variables were presented as sample counts (weighted percentages) and compared using the Rao-Scott chi-square test. Kaplan-Meier curves for all-cause and CVD mortality were plotted according to the LTWL grouping and compared using the log-rank test. Survey-weighted multivariable Cox proportional hazard regression models were used to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs) for the associations of LTWL with risk of all-cause and CVD mortality with no adjustment (crude model), adjustment for age, sex, race/ethnicity, marital status, education level, poverty-income ratio (model 1), and further adjustment for physical activity, waist circumferences, triglyceride, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, diabetes, hypertension, coronary heart disease, smoking, drinking, use of urate-lowering medications, uric acid levels, and historical maximum BMI (model 2). Subgroup analyses were performed to examine the association of LTWL with all-cause and CVD-specific mortality stratified by participants' age, sex, and comorbidities of hypertension, diabetes, and coronary heart disease, as previous studies have suggested that the presence of underlying comorbidities may modify the relationship between weight change and mortality risk [24]. Restricted cubic spline models based on the principle of the minimum Akaike information criterion were used to estimate the dose-response association of LTWL with all-cause and CVD mortality. To minimize reverse causation, we performed a sensitivity analysis by excluding participants who died within 24 months of follow-up. Statistical analyses were performed using R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) with the following packages: survey (for complex survey design), reshape 2 (data manipulation), survival (time-to-event analysis), ggplot2 (data visualization), and rms (regression modeling). A two-tailed Pvalue < 0.05 indicated statistical significance.

Results

Baseline characteristics

The baseline characteristics of the study participants, stratified by LTWL category, are summarized in Table 1. A total of 5,130 participants, with a mean age of 43.31 years, a male proportion of 63.86% and mean uric acid level of 7.51 mg/dL, were included. The mean historical maximum BMI, BMI from 1-year-ago, and current BMI were 35.69 kg/m^2, 32.93 kg/m^2, and 33.09 kg/m^2, respectively. Compared with the LTWL < 5% reference group, participants with LTWL ≥ 15% were significantly older, more likely to be female, economically disadvantaged, more likely to be single, more likely to be current smokers, with significantly lower waist circumference and higher physical activity, and more likely to have comorbidities of diabetes. Regarding laboratory findings, participants in the LTWL ≥ 15% group were associated with significantly higher high-density lipoprotein, as well as significantly lower total cholesterol and lower estimated glomerular filtration rate.

Kaplan-meier survival curves

During a median follow-up time of 113 (interquartile range 61–166) months, 505 all-cause (147 CVD-related) deaths have been recorded. The weighted percentage of all-cause mortality for the LTWL < 5%, 5-9.9%, 10-14.99% and ≥ 15% groups were 7.24%, 8.88%, 8.58% and 15.34%, respectively. The weighted percentage of CVD mortality for the LTWL < 5%, 5-9.9%, 10-14.99% and ≥ 15% groups were 1.71%, 3.17%, 3.41% and 5.25%, respectively.

The Kaplan-Meier survival curves for both all-cause and CVD mortality, stratified by LTWL groups, are presented in Fig. 2. We observed significantly lower overall survival rates (P < 0.001) and CVD-free survival rates (P < 0.001) among participants with higher LTWL compared to those with lower LTWL.

Table 1 Comparison of baseline characteristic of the study participants by categories of long-term weight loss

Characteristics	Long-term weight loss categories					*P* value
	Total (*n* = 5130)	< 5% (*n* = 3475)	5-9.9% (*n* = 933)	10-14.9% (*n* = 381)	≥ 15% (*n* = 341)	
Age, years	43.31 ± 0.23	43.00 ± 0.29	42.79 ± 0.47	45.72 ± 0.90	45.18 ± 0.91	0.01
Sex, n (%)						< 0.001
Male	3152 (63.86)	2128 (64.00)	621 (69.65)	235 (62.58)	168 (47.82)	
Female	1978 (36.14)	1347 (36.00)	312 (30.35)	146 (37.42)	173 (52.18)	
Race/ethnicity, n (%)						0.18
Non-Hispanic White	1377 (12.91)	926 (13.10)	265 (13.01)	95 (10.89)	91 (13.02)	
Non-Hispanic Black	2168 (68.32)	1426 (67.33)	397 (67.94)	177 (73.00)	168 (74.05)	
Mexican American	709 (6.83)	517 (7.33)	108 (6.13)	52 (6.28)	32 (4.37)	
Other Hispanic	370 (4.92)	255 (5.04)	68 (5.10)	26 (4.21)	21 (3.94)	
Other	506 (7.02)	351 (7.19)	95 (7.83)	31 (5.62)	29 (4.61)	
Poverty-income ratio	3.05 ± 0.04	3.10 ± 0.04	3.07 ± 0.07	2.95 ± 0.12	2.62 ± 0.12	0.002
Single marital status, n (%)	2021 (35.77)	1304 (34.10)	380 (38.49)	170 (37.82)	167 (48.05)	< 0.001
Education level, n (%)						0.30
< High school	371 (3.92)	273 (4.37)	50 (2.56)	30 (4.31)	18 (2.75)	
High school	2024 (36.92)	1359 (36.39)	360 (37.06)	154 (38.97)	151 (39.93)	
> High school	2732 (59.09)	1841 (59.24)	523 (60.39)	197 (56.72)	171 (57.33)	
Diabetes, n (%)	990 (14.71)	651 (14.53)	162 (11.59)	87 (17.65)	90 (21.91)	0.001
Hypertension, n (%)	2719 (49.46)	1807 (49.21)	483 (46.14)	230 (55.27)	199 (54.68)	0.06
Coronary heart disease, n (%)	179 (2.98)	111 (2.66)	36 (3.53)	16 (3.63)	16 (4.04)	0.49
Smoking, n (%)						< 0.001
Never	2648 (51.54)	1899 (54.27)	458 (50.28)	160 (41.59)	131 (39.18)	
Former	1295 (26.38)	866 (26.33)	230 (25.61)	112 (29.86)	87 (25.38)	
Current	1183 (22.03)	706 (19.41)	245 (24.11)	109 (28.55)	123 (35.44)	
Drinking, n (%)						0.04
Never	501 (8.33)	362 (9.59)	81 (8.12)	29 (6.40)	29 (8.04)	
Former	735 (12.81)	524 (14.65)	103 (10.83)	60 (14.63)	48 (12.33)	
Mild	1430 (30.15)	973 (33.40)	274 (31.65)	98 (31.29)	85 (26.73)	
Moderate	744 (14.86)	498 (15.46)	133 (16.50)	63 (18.15)	50 (17.87)	
Heavy	1309 (26.66)	857 (26.90)	252 (32.90)	100 (29.53)	100 (35.03)	
Urate-lowering medication use, n (%)	129 (2.17)	91 (2.30)	24 (2.73)	5 (0.44)	9 (1.25)	0.01
PA, Met-min/week	3628.56 ± 140.69	3366.42 ± 142.64	4294.34 ± 350.54	4091.29 ± 445.41	3804.83 ± 411.36	0.01
Waist circumference, cm	110.10 ± 0.36	111.64 ± 0.43	107.25 ± 0.61	105.99 ± 0.91	107.01 ± 1.31	< 0.001
Current weight, pounds	215.88 ± 1.03	221.20 ± 1.27	209.19 ± 1.87	199.71 ± 2.60	199.09 ± 3.14	< 0.001
Weight 1 year ago, pounds	214.90 ± 1.09	220.57 ± 1.29	207.28 ± 2.14	198.20 ± 2.57	197.92 ± 3.42	< 0.001
Historical maximum weight, pounds	232.74 ± 1.09	230.28 ± 1.29	229.30 ± 2.10	232.23 ± 3.03	267.45 ± 4.41	< 0.001
Current BMI, kg/m^2	33.09 ± 0.14	33.93 ± 0.18	31.71 ± 0.24	30.88 ± 0.36	31.05 ± 0.46	< 0.001
BMI 1 year ago, kg/m^2	32.93 ± 0.15	33.81 ± 0.18	31.42 ± 0.26	30.67 ± 0.38	30.83 ± 0.50	< 0.001
Historical maximum BMI, kg/m^2	35.69 ± 0.15	35.32 ± 0.18	34.77 ± 0.27	35.94 ± 0.45	41.74 ± 0.66	< 0.001
Triglyceride, mg/dL	195.70 ± 2.94	198.46 ± 3.53	190.91 ± 7.39	200.32 ± 9.34	176.20 ± 10.95	0.22
HDL, mg/dL	46.51 ± 0.27	45.38 ± 0.27	47.32 ± 0.62	48.94 ± 1.05	52.92 ± 1.29	< 0.001
Total cholesterol, mg/dL	203.86 ± 0.87	204.12 ± 1.02	204.37 ± 2.03	205.49 ± 2.49	198.07 ± 2.73	0.18
Uric acid, mg/dL	7.51 ± 0.02	7.53 ± 0.02	7.53 ± 0.03	7.52 ± 0.06	7.33 ± 0.07	0.09
eGFR, mL/min/1.73m^2	91.80 ± 0.40	92.53 ± 0.45	91.99 ± 0.86	88.65 ± 1.33	87.41 ± 1.54	0.01
Long-term weight loss (%)	4.51 ± 0.12	1.18 ± 0.04	7.03 ± 0.06	12.12 ± 0.10	22.42 ± 0.47	< 0.001

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; Met-min/week, weekly metabolic equivalents; PA, physical activity. P refers to the comparison among the LTWL < 5%, 5-9.9%, 10-14.9%, and ≥ 15% groups. Data are presented as mean ± standard error or counts (weighted percentage), as appropriate

Associations between LTWL and outcomes

As presented in Table 2, every 1% increase in LTWL was associated with a 4% increase in all-cause mortality and 5% increase in CVD mortality in the crude model. In the crude model, participants achieving ≥ 15% LTWL exhibited significantly higher risks of all-cause (HR = 2.89, 95% CI 2.02–3.81) and CVD mortality (HR = 4.02, 95% CI 2.28–7.08) relative to the LTWL < 5% reference group.

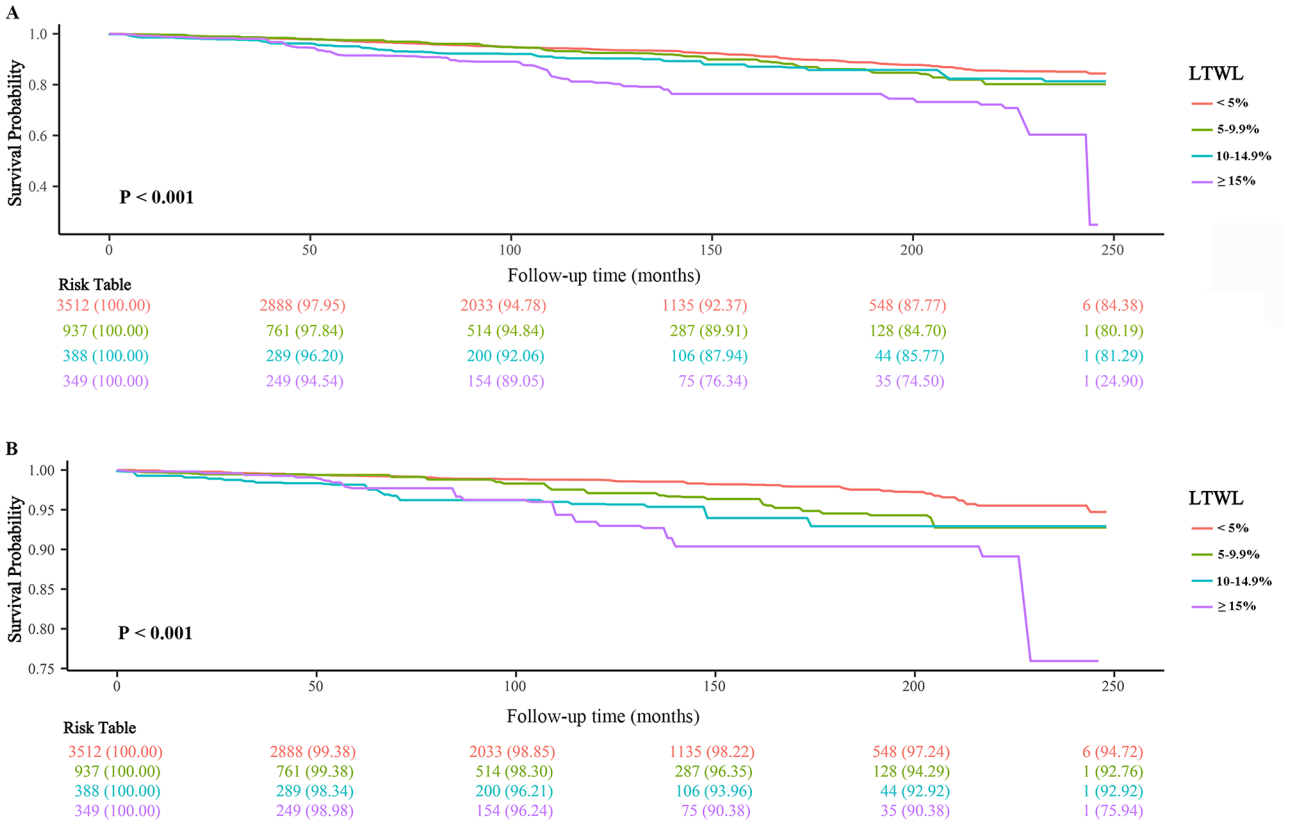

Fig. 2 Kaplan-Meier curves for the all-cause mortality (**A**) and cardiovascular disease mortality (**B**) in hyperuricemic participants with overweight or obesity stratified by different groups of long-term weight loss (LTWL)

Table 2 Associations of long-term weight loss with all-cause and cardiovascular mortality in hyperuricemic patients with overweight or obesity

	Crude model		Model 1		Model 2	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
All-cause mortality						
LTWL (per 1%)	1.04 (1.03, 1.06)	< 0.001	1.03 (1.01, 1.04)	0.002	1.02 (1.00, 1.04)	0.05
LTWL category						
< 5%	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
5-9.9%	1.23 (0.90, 1.69)	0.20	1.13 (0.80, 1.59)	0.49	1.11 (0.72, 1.71)	0.63
10-14.9%	1.45 (0.97, 2.16)	0.07	1.15 (0.78, 1.70)	0.48	1.34 (0.79, 2.26)	0.27
≥ 15%	2.77 (2.02, 3.81)	< 0.001	2.10 (1.46, 3.02)	< 0.001	1.82 (1.14, 2.92)	0.01
P for trend	< 0.001		< 0.001		0.02	
Cardiovascular mortality						
LTWL (per 1%)	1.05 (1.03,1.07)	< 0.0001	1.04 (1.01, 1.06)	0.002	1.04 (1.00, 1.08)	0.05
LTWL category						
< 5%	1 (Reference)	/	1 (Reference)	/	1 (Reference)	/
5-9.9%	1.82 (0.99, 3.33)	0.05	1.81 (0.99, 3.32)	0.06	1.83 (0.76, 4.43)	0.18
10-14.9%	2.64 (1.48, 4.73)	0.001	2.10 (1.16, 3.82)	0.01	2.15 (0.76, 6.10)	0.15
≥ 15%	4.02 (2.28, 7.08)	< 0.001	3.06 (1.68, 5.58)	< 0.001	3.76 (1.51, 9.36)	0.004
P for trend	< 0.001		< 0.001		0.003	

CI, confidence interval; HR, hazard ratio; LTWL, long-term weight loss

Model 1 was adjusted for age, sex, race/ethnicity, marital status, education level, and poverty-income ratio; Model 2 was further adjusted for physical activity, waist circumferences, triglyceride, total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, diabetes, hypertension, coronary heart disease, smoking, drinking, use of urate-lowering medications, uric acid levels, and historical maximum body mass index

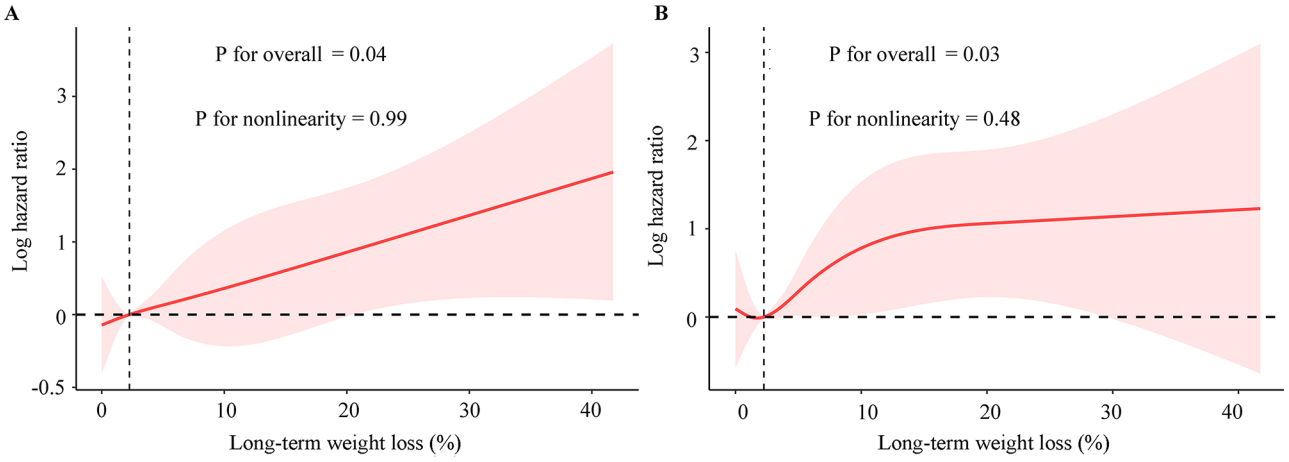

Fig. 3 Restricted cubic spline analysis showing the dose-response relationships between long-term weight loss and mortality from all-cause (**A**) and cardiovascular disease (**B**). The shadow represents the 95% confidence interval

Table 3 Subgroup analysis for the associations between long-term weight loss and all-cause mortality

LTWL	< 5%	5-9.9%	*P*	10–14.9%	*P*	≥ 15%	*P*	*P* for interaction
Age, years								0.57
< 45	Ref.	1.14 (0.55, 2.37)	0.72	0.40 (0.11, 1.48)	0.17	2.07 (0.70, 6.13)	0.19	
≥ 45	Ref.	1.18 (0.79, 1.74)	0.42	1.18 (0.73, 1.92)	0.50	2.35 (1.52, 3.63)	< 0.001	
Sex								0.008
Male	Ref.	0.82 (0.47, 1.42)	0.48	0.83 (0.39, 1.77)	0.63	0.99 (0.52, 1.87)	0.97	
Female	Ref.	1.74 (0.84, 3.58)	0.14	2.38 (1.05, 5.39)	0.04	2.67 (1.36, 5.28)	0.005	
Diabetes								0.10
No	Ref.	1.27 (0.86, 1.88)	0.24	0.97 (0.55, 1.72)	0.92	2.85 (1.74, 4.67)	< 0.001	
Yes	Ref.	1.05 (0.51, 2.16)	0.90	1.20 (0.57, 2.52)	0.63	1.37 (0.55, 3.39)	0.50	
Hypertension								0.94
No	Ref.	1.29 (0.71, 2.35)	0.40	0.96 (0.45, 2.05)	0.91	2.12 (0.81, 5.50)	0.12	
Yes	Ref.	1.11 (0.74, 1.68)	0.62	1.10 (0.65, 1.87)	0.71	2.49 (1.50, 4.14)	< 0.001	
Coronary heart disease								0.56
No	Ref.	1.16 (0.80, 1.68)	0.45	1.09 (0.68, 1.76)	0.72	2.12 (1.33, 3.38)	0.002	
Yes	Ref.	1.10 (0.36, 3.38)	0.87	0.92 (0.22, 3.93)	0.92	6.23 (2.46, 15.82)	< 0.001	

Trend tests showed that in model 2, compared with the LTWL < 5% group, the HRs (95%CI) for LTWL 5-9.9%, 10-14.9%, and ≥ 15% groups were 1.11 (0.72–1.71), 1.34 (0.79–2.26), and 1.85 (1.14–2.92) for all-cause mortality (P for trend = 0.02), and 1.83 (0.76–4.43), 2.15 (0.76–6.10), and 3.76 (1.51–9.36) for CVD mortality (P for trend = 0.003), respectively.

Restricted cubic spline analysis showed linear associations between LTWL and all-cause or CVD mortality (Fig. 3).

Subgroup analysis

Subgroup analysis (Table 3**and** Table 4) showed that participants' age and comorbidities of diabetes, hypertension and coronary heart disease did not influence the associations between LTWL and all-cause or CVD mortality. Nonetheless, significant associations between all-cause (P for interaction = 0.008) and CVD (P for interaction = 0.02) mortality were observed exclusively in female participants, with no significant associations found in male participants.

Sensitivity analysis

Sensitivity analysis (Supplementary Table 1), in which participants died within 24 months of follow-up were excluded, demonstrated that the results remained robust and were not significantly altered.

Discussion

Overall, using large and nationally representative data, we demonstrated that prior LTWL is associated with an increased all-cause and CVD mortality among US adults with hyperuricemia. There were approximately linear dose-response associations of higher LTWL with increased risk of all-cause and CVD mortality. Interestingly, this association was observed exclusively in female participants, not in male participants. The findings of this study highlighted a significant sex-specific difference in

Table 4 Subgroup analysis for the associations between long-term weight loss and cardiovascular disease mortality

LTWL	< 5%	5-9.9%	*P*	10–14.9%	*P*	≥ 15%	*P*	*P* for interaction
Age, years								NA
< 45	Ref.	1.95 (0.67, 5.69)	0.22	0.76 (0.16, 3.67)	0.73	NA	NA	
≥ 45	Ref.	1.78 (0.85, 3.74)	0.13	2.87 (1.26, 6.55)	0.01	5.99 (2.47, 14.50)	< 0.001	
Sex								0.02
Male	Ref.	1.54 (0.78, 3.04)	0.22	1.08 (0.45, 2.58)	0.86	3.84 (1.54, 9.56)	0.004	
Female	Ref.	3.23 (1.16, 8.96)	0.03	6.65 (2.11, 21.01)	0.001	6.28 (1.51, 26.06)	0.01	
Diabetes								0.16
No	Ref.	1.86 (0.93, 3.73)	0.08	1.27 (0.42, 3.87)	0.68	4.37 (1.61, 11.87)	0.004	
Yes	Ref.	2.28 (0.78, 6.68)	0.14	4.02 (1.52, 10.65)	0.005	1.91 (0.60, 6.08)	0.27	
Hypertension								0.85
No	Ref.	2.28 (0.87, 5.98)	0.10	1.55 (0.29, 8.20)	0.61	7.24 (1.65, 31.77)	0.009	
Yes	Ref.	1.86 (0.95, 3.64)	0.07	2.41 (1.09, 5.32)	0.03	3.18 (1.24, 8.16)	0.02	
Coronary heart disease								0.81
No	Ref.	1.76 (0.95, 3.26)	0.07	2.13 (0.95, 4.78)	0.07	3.16 (1.39, 7.21)	0.006	
Yes	Ref.	9.22 (3.12, 27.22)	< 0.001	3.57 (0.28, 45.05)	0.33	13.69 (2.05, 91.39)	0.007	

NA, not applicable

the association between LTWL and mortality, emphasizing the potential risks of weight loss in the female population and calling for the initiation of rigorous prospective studies to provide high-level evidence for guiding weight loss counseling in clinical practice.

Prior studies have consistently observed a beneficial effect of weight loss on uric acid control in patients with hyperuricemia or gout, for which weight loss is frequently recommended for patients with hyperuricemia. Nonetheless, no studies have yet examined whether prior weight loss could modify the mortality risk in individuals with hyperuricemia. A study by Maglio et al. showed that obese patients undergoing bariatric surgery had a 53% reduced risk of hyperuricemia [25]. Another nationwide cohort study also demonstrated that participants with a weight loss of ≥ 4 kg had a 56% lower risk of hyperuricemia as compared to subjects with stable adiposity status [26]. A recent meta-analysis of 20 studies involving 5,233 gout patients showed that weight loss from bariatric surgery was associated with a mean decrease in serum uric acid of 1.91 mg/dL at 3-year follow-up [27]. Accumulating evidence suggests that successful LTWL (≥ 5%) is associated with a more favorable uric acid profile among overweight/obese individuals. It should be noted, however, that the majority of existing studies evaluating the effect of weight loss on hyperuricemia/gout have primarily focused on uric acid changes and gout flares, with little attention paid to long-term mortality outcomes.

Compatible with a prior study examining correlates of intentional weight loss [28], we also found that several socioeconomic characteristics were associated with increasing LTWL, such as older age, female predominance, lower economic status, and single status. Moreover, the proportions of participants with comorbid diabetes and hypertension also differed significantly across different LTWL groups.

The study results indicated a positive association between LTWL and increased risks of all-cause and CVD mortality in individuals with hyperuricemia, which aligns with some prior studies but contradicts others in the general population. For instance, Zhang and colleagues showed in a sample of 433,829 individuals that weight loss was associated with 25% and 17% increased risk of all-cause and CVD mortality, respectively, compared with individuals with stable weight [29]. In a prospective study of 19,114 healthy elderly, Hussain et al. demonstrated that participants with LTWL 5–10% and > 10% had 33% and 289% higher risk of all-cause mortality in men and 26% and 114% higher risk in women, respectively [30]. In comparison, a prospective work reported a significant reduction in the risk of all-cause mortality for intentional weight loss of at least 5 pounds in 161,738 middle-aged adults, which was positively correlated with the frequency of weight loss attempts [31]. Weight fluctuations have been proposed as a plausible explanation for the inconsistent findings between the current study and that by Willis et al. [31], as approximately 65–80% of adults who intentionally lose weight will regain some, if not all, of the lost weight within 1 year after discontinuing treatment [32]. In another prospective cohort study with a median follow-up of 17 years, Maru et al. observed that extreme weight gain or weight loss, defined as weight change ≥ 15% within 1 year was not statistically significantly associated with subsequent higher mortality [33]. Of note, the participants in the majority of these studies were heterogeneous and did not specifically focus on participants with overweight or obesity.

Notably, the inconsistent results may arise from several key factors that have been previously reported to

confound the associations between LTWL and mortality risk. Specifically, non-elderly and elderly adults appear to differ in the sense that weight loss in the latter may reflect loss of muscle mass or sarcopenia, with subsequent increased risk of frailty and mortality [34]. Weight loss in patients with different baseline weight status also has distinct implications, as studies have found that underweight individuals have a significantly increased risk of mortality due to malnutrition or poor control of underlying chronic conditions [35]. Our study circumvented these problems by focusing on community-dwelling hyperuricemic individuals who were overweight or obese and by restricting the study population to the non-elderly adults.

The restricted cubic spline analysis showed linear associations between LTWL and all-cause or CVD mortality. However, the specific mechanisms underlying these associations remain poorly understood. It could be argued that, weight loss, particularly excessive weight loss, may indicate the presence of an underlying illness, which in turn may be responsible for the unfavorable outcome [36]. Another plausible explanation for this association is that weight loss is associated with increased cytokine release and impaired immunity, both of which could lead to premature mortality [37]. Finally, weight loss may trigger the release of lipophilic chemicals stored in the adipose tissue, leading to higher serum concentrations of persistent organic pollutants and higher mortality [38]. Persistent organic pollutants are known endocrine disruptors released during weight loss that can promote inflammation, induce mitochondrial and β-cell dysfunction, and alter thyroid hormone levels [39].

An intriguing finding of the present study is that the associations between LTWL and all-cause or CVD-specific mortality were restricted to female participants. This finding, nonetheless, contrasts with several prior studies in the general obese population with gender-stratified results. For instance, Beiglböck et al. demonstrated that the long-term mortality rate was significantly higher in men than in women for those who underwent bariatric surgery for morbid obesity [40]. Similarly, in the general elderly population, Alharbi and colleagues found that the increased mortality risk associated with weight loss was observed only in men, but not in women [41]. In contrast, two previous studies reported that the effect of weight loss on mortality in the general population or older adults was similar in men and women [42, 43]. This gender disparity may be attributed to distinct differences in body composition, fat distribution, and physiological responses to weight loss. Women typically exhibit higher percentages of body fat and lower lean muscle mass compared to men [44]. In addition, studies have also consistently demonstrated that men experience greater absolute weight loss than women [45]. Consequently, with the same LTWL, women may lose a greater proportion of lean muscle mass relative to fat mass than men, which may potentially explain the higher all-cause and CVD mortality rate observed in women. Notably, our study revealed that women were more likely to have extreme weight loss, as indicated by LTWL ≥ 15%, a factor we hypothesize may further contribute to their increased mortality risk. In addition, emerging evidence have also indicted that men and women responded differently to rapid weight loss, with women had higher reductions in fat-free mass and larger reductions in high-density lipoprotein cholesterol [46], which may collectively account for the disproportionately higher mortality risk observed in women with equivalent LTWL.

The strengths of this study include the application of nationally representative data, with a focus on hyperuricemic non-elderly adults. In addition, we have controlled for a variety of potential confounders and performed sensitivity analysis to obtain more convincing results. However, this study also suffers from several limitations that must be acknowledged. First, the current study defined overweight or obesity using pre-baseline historical maximum BMI, and hyperuricemia was diagnosed at baseline, making it difficult to determine whether weight loss preceded or followed the onset of hyperuricemia. In addition, data on historical maximum weight and weight 1 year ago were collected by self-report, which may potentially introduce recall bias. Nonetheless, prior studies have reported that recall bias of historical weights was minimal [47]. Second, although historical maximum weight and weight 1 year ago is the most commonly used method, it neglects the trajectory of weight loss fluctuations over time. In addition, this study did not account for the rate of weight loss. A previous meta-analysis demonstrated that, compared to rapid weight loss, gradual weight loss was associated with greater reductions in fat mass and body fat percentages [48]. Therefore, the rate of weight loss (rapid vs. gradual) may differentially influence mortality risk. Third, we did not distinguish participants with intentional weight loss from those whose weight loss was unintentional, as it is frequently difficult to accurately distinguish these two scenarios in observational studies [49]. Finally, the exact interventions or approaches employed by respondents to achieve the LTWL were not considered in the study.

Conclusion

In conclusion, our study found that ≥ 5% LTWL was associated with increased all-cause and CVD mortality in US non-elderly female hyperuricemic participants, a phenomenon not found in male counterparts. Additional prospective and longitudinal randomized clinical trials are necessary to further examine this sex-specific associations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-025-00930-3.

Supplementary Material 1

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None.

Author contributions
Wei Wang designed the research and performed data analysis. Yanshan Li and Xiufang Kong wrote the paper. All authors reviewed the manuscript.

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Data availability
The dataset was based on the NHANES, which is publicly available and could be found below: https://www.cdc.gov/nchs/nhanes/.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This study was conducted according to the guideline laid down in the Declaration of Helsinki. This study used data from NHANES, a public database that can be freely accessed. The NHANES protocol and procedures were approved by the National Center for Health Statistics Institutional Review Board, and all adult participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
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