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Original article

The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial

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Abstract

Objectives. To evaluate the person-level impact of weight loss on serum urate levels among men with a high cardiovascular risk profile.

Methods. We analysed 12 379 men (mean serum urate level = 407 µmol/l) from the Multiple Risk Factor Intervention Trial, using data prospectively collected at baseline and annually over a 7-year period (78 881 visits). Our endpoint was normouricaemia, defined by serum urate levels $\leqslant 360$ µmol/l, a widely accepted therapeutic target. Person-level effects were estimated using conditional logistic regression models to adjust for time-varying covariates (age, congestive heart failure, hypertension, diuretic use, renal function, alcohol intake and dietary factors).

Results. There was a graded relation between weight loss and achieving normouricaemia (*P*-value for trend <0.001). Compared with no weight change (−0.9 to 0.9 kg), the multivariate odds ratios of achieving normouricaemia for a weight loss of 1–4.9, 5–9.9 and $\geqslant 10$ kg were 1.43 (95% CI: 1.33, 1.54), 2.17 (1.95, 2.40) and 3.90 (3.31, 4.61), respectively. The corresponding serum urate level changes were −7, −19 and −37 µmol/l (−0.12, −0.31 and −0.62 mg/dl). Similar levels of associations persisted among subgroups stratified by demographics, presence of gout, hypertension, diuretic use, renal insufficiency, alcohol intake, trial group assignment and adiposity categories (all *P*-values for trend <0.001).

Conclusions. Weight reduction could help achieve a widely accepted therapeutic urate target level ($\leqslant 360$ µmol/l) among men with a high cardiovascular risk profile. Although the urate-lowering effect appeared weaker than that of urate-lowering drugs, other associated health benefits would make weight reduction important, particularly in this population.

Key words: Weight loss, Serum urate, Gout.

Introduction

Hyperuricaemia is the precursor of gout, a common and excruciatingly painful inflammatory arthritis [1, 2]. Furthermore, hyperuricaemia is associated with several major conditions, including cardiovascular disorders [3, 4], end-stage renal disease [5], the metabolic syndrome [6] and type 2 diabetes [7].

Adiposity is a prominent determinant for hyperuricaemia and gout [8–13]. Prospective cohort studies have found a strong relation between higher adiposity (or weight gain) and both hyperuricaemia and an increased risk of incident gout [8–13]. Although these data suggest that weight loss would lower uric acid levels and the risk of gout, the specific data on the impact of weight loss are limited, likely due to the fact that most adult participants of observational studies tend not to experience weight loss with ageing [10]. A few small, open-label intervention studies (*n* = 27 [14], *n* = 13 [15]) have suggested that weight reduction is associated with a decline in serum urate levels. However, no large-scale prospective data are available on the impact of weight loss on serum urate levels, particularly after adjusting for potential confounders such as hypertension, diuretic use, congestive heart failure, renal

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function, alcohol intake and dietary factors, which tend to vary with weight change and affect serum urate levels [9, 16–18]. Since overweight and obesity are epidemic and their prevalence continues to rise [19], and weight is an important modifiable risk factor for hyperuricaemia and gout, an accurate understanding of its impact is essential.

To address these issues, we performed a longitudinal analysis of 12 379 men (mean serum urate level = 407 μmol/l) with a high cardiovascular risk profile in the Multiple Risk Factor Intervention Trial (MRFIT), where a large number of participants experienced weight loss during a 7-year follow-up period. In this study, we viewed weight loss as a therapeutic modality in a given individual and focused on the person-level (as opposed to population-level) impact of weight loss on achieving a widely accepted therapeutic target of serum urate levels ⩽360 μmol/l (6 mg/dl) [20–22].

Methods

Study population

The MRFIT study was a large collaborative randomized clinical trial designed to evaluate the effect of multiple risk factor intervention on mortality rate from coronary heart disease among high-risk men. Detailed descriptions of the MRFIT have been published elsewhere [23–25]. Subjects were eligible if scores for the combination of three risk factors (smoking, hyperlipidaemia and hypertension) were sufficiently high to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study [26]. The intervention programme of the MRFIT included smoking cessation, weight reduction (in men ⩾115% of desirable weight) by caloric intake reduction and increased physical activity, nutritional counselling (to reduce saturated fat and dietary cholesterol consumption and increase polyunsaturated fat intake), and anti-hypertensive treatment with hydrochlorothiazide or chlorthalidone [23].

Between 1973 and 1976, the MRFIT investigators screened 361 662 men for eligibility at 22 different clinical centres. Of this group, 12 866 men between the ages of 35 and 57 years were randomly assigned to either a special intervention group (*n* = 6428) or a usual care group (*n* = 6438). Participants were followed for seven annual visits and the follow-up rate was >90%.

We included 12 379 men (78 881 visits) who had a baseline screening visit, had at least one annual follow-up visit and had complete data from these visits for serum urate level (outcome), weight (exposure) and other covariates (i.e. age, race, education level, congestive heart failure, hypertension, diuretic use, serum creatinine level, alcohol intake and dietary variables). Ethical approval for the present study was obtained from Boston University Medical Center.

Assessment of serum urate levels and primary endpoint

Serum urate levels and other laboratory tests, including lipid profiles, blood glucose levels and blood chemistry tests, were performed at baseline and annually thereafter [27]. Blood samples were sent to a central laboratory for analysis, and the results were determined as previously described [27]. Our endpoint was normouricaemia defined by serum urate levels ⩽360 μmol/l (6 mg/dl), a widely accepted therapeutic target [20–22], as we treated weight loss as a potential therapeutic (or preventive) modality in the current study. We also examined the potential impact on an alternative definition of endpoint {serum urate levels ⩽420 μmol/l (7 mg/dl), a cut-off value for presence of hyperuricaemia among men [28]}.

Assessment of weight and other covariates

At baseline, and every subsequent year, subjects provided a detailed medical history, including medication and social histories, and underwent a full physical examination including weight measurements. Procedures for the visits, including methods for measuring weight and other covariates, have been described in detail previously [23, 24]. Standard and random-zero blood pressure measurements were recorded as the average of two measurements. Hypertension was defined as systolic blood pressure ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg or use of anti-hypertensive medications at each visit [29]. BMI was calculated as the weight in kilograms divided by the square of the height in metres. In the MRFIT, 24-h dietary recalls were obtained at baseline and during follow-up visits [30–32]. Glomerular filtration rate (GFR) was estimated using the simplified modification of diet in renal disease study equation [18, 33–35]: GFR (ml/min/1.73 m^2) = 186 × [serum creatinine level (mg/dl)]$^{-1.154}$ × (age)$^{-0.203}$ × [1.212, if African American]. We used a case definition of gout based on an affirmative answer to the question, 'Have you been told by your physician that you have gout?' [7, 36].

Statistical analyses

We categorized baseline BMI into six groups (<21, 21–22.9, 23–24.9, 25–29.9, 30–34.9 and ⩾35 kg/m^2) and categorized weight change from weight at baseline into six groups: ⩾10 kg loss, 5–9.9 kg loss, 1–4.9 kg loss, no change (−0.9 to 0.9 kg), 1–4.9 kg gain, 5–9.9 kg gain and ⩾10 kg gain. We assessed the longitudinal person-level impact of weight loss on achieving normouricaemia status, using person-specific logistic regression models conditioned on each participant (i.e. conditional logistic regression). This approach provides estimates that are statistically equivalent to those from generalized (non-linear) mixed models [37], and is computationally more efficient. In these person-specific analyses (conditioned on each participant), potential time-fixed confounders that vary between individuals, including unmeasured ones, are eliminated implicitly by the study design, as one visit in a given person is compared with another visit within the same person. Thus, these models were adjusted only for time-varying covariates [age (continuous), congestive heart failure (yes or no), hypertension (yes or no), diuretic use (yes or no), serum creatinine level (continuous), alcohol intake (continuous) and dietary

variables (intakes of fructose, caffeine, total protein, poly-unsaturated fat, monounsaturated fat, saturated fat and fibre)]. For analyses using serum urate levels as a continuous outcome, we used linear mixed models additionally adjusting for baseline covariates [race (African American *vs* Caucasian), education level (>12 *vs* ⩽12 Grade) and weight categories (<70, 70–74.9, 75–79.9, 80–84.9, 85–89.9, 90–94.9, 95–99.9, 100–104.9, 105–109.9 and ⩾110 kg)]. Trends in achieving normouricaemia status (or serum urate levels as continuous variable) in relation to weight change were assessed by using the continuous values of weight change.

We performed subgroup analyses stratified by demographics [age ⩽47 (median) *vs* >47 years; Caucasian *vs* African American; ⩽12 Grade education *vs* higher], the presence of gout (no *vs* yes), hypertension (no *vs* yes), diuretic use (no *vs* yes), renal insufficiency (GFR ⩽60 *vs* >60 ml/min/1.73 m^2), alcohol intake (no *vs* yes), trial group assignment (special intervention group *vs* usual care group) and BMI categories (<25, 25–29.9 and ⩾30 kg/m^2) by using the final multivariate model. For all odds ratios (ORs) and difference estimates, we calculated 95% CIs. All *P*-values were two sided. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

The mean baseline age of the participants was 46 years. The mean serum urate level was 407 μmol/l, with 70% of participants having a serum urate level >360 μmol/l and 38% having a serum urate level >420 μmol/l. The characteristics of the cohort are shown according to baseline BMI and weight change categories (Table 1). As expected, participants who were heavier at baseline were more likely to lose more weight. African Americans or less-educated participants tended to be either underweight or overweight. The proportion of baseline hypertension tended to increase as baseline BMI increased, and this proportion was higher among men who experienced weight loss during the follow-up. Alcohol intake tended to decrease with increasing baseline BMI, whereas protein intake tended to increase with increasing baseline BMI.

Impact of weight loss on serum urate levels

During the 7 years of follow-up, 74% of participants experienced weight loss. There was a graded association between weight loss and the presence of normouricaemia (*P*-value for trend <0.001) (Table 2). After adjusting for covariates, including time-varying age, congestive heart failure, hypertension, diuretic use, renal function, alcohol intake and dietary factors, the association remained strong with a similar magnitude (*P*-value for trend <0.001). Compared with no weight change (−0.9 to 0.9 kg), the multivariate ORs of achieving normouricaemia associated with weight loss of 1–4.9, 5–9.9 and ⩾10 kg were 1.43 (95% CI: 1.33, 1.54), 2.17 (95% CI: 1.95, 2.40) and 3.90 (95% CI: 3.31, 4.61), respectively (Table 2).

TABLE 1 Baseline characteristics according to baseline BMI (kg/m^2) and weight change from baseline (kg)

	Number of participants	Age, years	African American, %	Education (>12 grade), %	Weight, kg	Diuretic use, %	Hypertension, %	Creatinine, μmol/l	Alcohol, servings/week	Fructose, g/day	Caffeine, g/day	Protein, g/day	Saturated fat, g/day
Baseline BMI, kg/m^2													
<21	193	47	11	59	61	15	63	91.8	14	18	0.50	91	39
21–22.9	570	47	9	64	69	18	69	94.1	15	21	0.43	91	37
23–24.9	1789	47	6	67	75	17	68	96.0	13	20	0.44	90	37
25–29.9	6887	47	6	64	85	18	74	97.3	12	20	0.45	93	36
30–34.9	2543	46	9	60	98	18	76	98.4	12	20	0.44	96	38
⩾35	397	45	9	53	112	16	79	97.2	11	21	0.41	103	41
Weight change from baseline,[a] kg													
Loss ⩾10	412	46	6	62	96	13	82	97.8	13	21	0.44	96	37
Loss 5–9.9	1334	47	7	62	90	17	80	97.5	12	21	0.41	93	36
Loss 1–4.9	2866	47	7	64	85	16	75	97.3	12	20	0.43	92	36
No change (−0.9 to 0.9)	4175	46	8	62	84	18	72	97.3	13	20	0.45	93	37
Gain 1–4.9	2479	46	7	64	85	19	71	97.0	12	20	0.46	93	37
Gain 5–9.9	883	45	8	65	87	18	69	95.9	13	20	0.47	96	39
Gain ⩾10	230	45	7	67	90	19	62	95.4	12	19	0.55	93	38
All participants	12379	46	7	63	86	17	73	97.1	13	20	0.45	93	37

Baseline characteristics

aWeight changes were based on a randomly selected visit per participant because each participant contributed multiple visits.

TABLE 2 ORs of achieving serum urate levels $\leqslant 360 \, \mu$mol/l according to categories of weight change (kg)

Weight change from baseline, kg	Number of visits, %	Univariate OR (95% CI)	Multivariate OR[a] (95% CI)	Multivariate OR[b] (95% CI)
Loss $\geqslant$10	2837 (3.60)	4.00 (3.45, 4.65)	3.84 (3.26, 4.53)	3.90 (3.31, 4.61)
Loss 5–9.9	8511 (10.79)	1.94 (1.77, 2.13)	2.11 (1.90, 2.33)	2.17 (1.95, 2.40)
Loss 1, 4.9	19 055 (24.16)	1.29 (1.21, 1.37)	1.40 (1.31, 1.51)	1.43 (1.33, 1.54)
No change (−0.9 to 0.9)	25 475 (32.30)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Gain 1–4.9	15 951 (20.22)	0.72 (0.67, 0.77)	0.75 (0.69, 0.81)	0.75 (0.70, 0.82)
Gain 5–9.9	5502 (6.98)	0.39 (0.35, 0.44)	0.42 (0.37, 0.48)	0.43 (0.38, 0.49)
Gain $\geqslant$10	1550 (1.96)	0.30 (0.24, 0.38)	0.35 (0.27, 0.45)	0.35 (0.27, 0.45)
P-value for trend		<0.001	<0.001	<0.001

[a]Conditional logistic regression adjusted for time-varying covariates (i.e. age, congestive heart failure, hypertension, diuretic use and serum creatinine levels). [b]Conditional logistic regression further adjusted for time-varying alcohol intake and dietary factors (i.e. intakes of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre). Further adjustment of baseline covariates (i.e. weight, race and education level) did not change these multivariate OR estimates, as these time-fixed variables are implicitly adjusted by these models (see text for details).

The multivariate OR of normouricaemia per 1-kg weight loss was 1.11 (95% CI: 1.10, 1.12). Similarly, a graded association was observed with serum urate levels as a continuous outcome (Table 3). Compared with no weight change (−0.9 to 0.9 kg), the multivariate serum urate level differences associated with weight loss of 1–4.9, 5–9.9 and $\geqslant$10 kg were −7 (95% CI: −9, −6), −19 (95% CI: −20, −17) and −37 (95% CI: −40, −35) μmol/l, respectively (Table 3). The corresponding values in mg/dl were −0.12 (95% CI: −0.14, −0.11), −0.31 (95% CI: −0.34, −0.29) and −0.62 (95% CI: −0.66, −0.58).

An alternative definition of endpoint (serum urate levels $\leqslant$420 μmol/l) did not materially alter these results (Table 4). Compared with no weight change (−0.9 to 0.9 kg), the multivariate ORs for weight loss of 1–4.9, 5–9.9 and $\geqslant$10 kg were 1.30 (95% CI: 1.22, 1.39), 1.86 (95% CI: 1.69, 2.05) and 3.66 (95% CI: 3.11, 4.30), respectively. The multivariate OR of achieving serum urate levels $\leqslant$420 μmol/l/1 kg weight loss was 1.09 (95% CI: 1.08, 1.10).

The similarly strong magnitudes of association between weight loss and achieving normouricaemia persisted in all subgroups (all *P*-values for trend <0.001) stratified by demographic variables (age, race and education level), presence of gout, hypertension, diuretic use (no *vs* yes), renal insufficiency (GFR $\leqslant$60 *vs* >60 ml/min/1.73 m^2), alcohol intake (no *vs* yes), trial group assignment (with or without special intervention) and BMI categories (<25, 25–29.9 and $\geqslant$30 kg/m^2) (Table 5).

Discussion

In this large prospective cohort of men with a high cardiovascular risk profile and often with elevated serum urate levels, we found that weight loss led to a significant urate reduction. The effect increased with increasing weight loss with a clear dose–response relationship and, in a given individual, weight loss of $\geqslant$10 kg increased the odds of achieving serum urate level $\leqslant$360 μmol/l by nearly 4-fold. Overall, a 1-kg weight loss was associated with 11% increased odds of achieving the therapeutic goal. These associations were independent of other purported risk factors, including time-varying ones such as age, diuretic use, hypertension, congestive heart failure, renal function, alcohol intake and dietary factors. These associations persisted regardless of whether one had gout, and also persisted in subgroups stratified by baseline demographic variables, hypertension, diuretic use, renal insufficiency, alcohol intake, trial group assignment and BMI categories. These findings indicate that weight reduction can lead to a meaningful decrease in the risk of hyperuricaemia in men with a high cardiovascular risk profile, who often tend to have hyperuricaemia or gout.

These results extend upon previous studies that have examined the relation between adiposity and gout or hyperuricaemia by focusing on the impact of weight loss. A number of cohort studies have reported associations between increased adiposity (or weight gain) and the risk of gout or hyperuricaemia [8–13]. In addition, the Health Professionals Follow-up Study [10] reported that men who had lost $\geqslant$10 lb (4.5 kg) had a 39% lower risk of incident gout compared with men who had maintained weight [±4 lb (1.8 kg)] (95% CI: 0.40, 0.92) [10]. Similarly, in a Swedish Bariatric Surgery Outcome study, gastric surgery-induced weight reduction was associated with 78 and 51% lower odds of hyperuricaemia [urate level $\geqslant$450 μmol/l (7.6 mg/dl) in men and $\geqslant$340 μmol/l (5.7 mg/dl) in women] at 2 and 10 years after the surgery, respectively [38]. These findings agree well with the current data, although our results are based on the endpoints of achieving a widely accepted urate target level of 360 μmol/l [20–22]. Together with these previous findings, the present study provides quantitative evidence to support the current recommendation for weight reduction in the management of hyperuricaemia [39, 40]. As the

TABLE 3 Changes in serum urate levels (μmol/l) according to categories of weight change (kg)

Weight change from baseline, kg	Number of visits, %	Unadjusted change (95% CI)	Multivariate change[a] (95% CI)	Multivariate change[b] (95% CI)
Loss ⩾10	2837 (3.60)	−34 (−37, −31)	−37 (−40, −35)	−37 (−40, −35)
Loss 5–9.9	8511 (10.79)	−13 (−14, −11)	−18 (−20, −17)	−19 (−20, −17)
Loss 1–4.9	19 055 (24.16)	−3 (−4, −2)	−7 (−8, −6)	−7 (−9, −6)
No change (−0.9 to 0.9)	25 475 (32.30)	0 (Referent)	0 (Referent)	0 (Referent)
Gain 1–4.9	15 951 (20.22)	9 (7, 10)	6 (5, 7)	5 (4, 7)
Gain 5–9.9	5502 (6.98)	23 (21, 25)	18 (16, 20)	17 (16, 19)
Gain ⩾10	1550 (1.96)	34 (31, 38)	26 (23, 30)	26 (23, 29)
P-value for trend		<0.001	<0.001	<0.001

[a]Linear mixed model adjusted for baseline covariates (race, education level and weight categories), and time-varying covariates (i.e. age, congestive heart failure, hypertension, diuretic use and serum creatinine levels). [b]Linear mixed model further adjusted for time-varying alcohol intake and dietary factors (i.e. intakes of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre).

TABLE 4 ORs of achieving serum urate levels ⩽420 μmol/l according to categories of weight change (kg)

Weight change from baseline, kg	Number of visits, %	Univariate OR (95% CI)	Multivariate OR[a] (95% CI)	Multivariate OR[b] (95% CI)
Loss ⩾10	2837 (3.60)	3.16 (2.73, 3.66)	3.54 (3.01, 4.15)	3.66 (3.11, 4.30)
Loss 5–9.9	8511 (10.79)	1.47 (1.35, 1.60)	1.79 (1.63, 1.96)	1.86 (1.69, 2.05)
Loss 1–4.9	19 055 (24.16)	1.08 (1.02, 1.14)	1.26 (1.18, 1.35)	1.30 (1.22, 1.39)
No change (−0.9 to 0.9)	25 475 (32.30)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Gain 1–4.9	15 951 (20.22)	0.69 (0.65, 0.74)	0.76 (0.71, 0.82)	0.77 (0.72, 0.83)
Gain 5–9.9	5502 (6.98)	0.41 (0.37, 0.45)	0.47 (0.42, 0.52)	0.47 (0.42, 0.53)
Gain ⩾10	1550 (1.96)	0.29 (0.24, 0.35)	0.37 (0.30, 0.45)	0.38 (0.31, 0.46)
P-value for trend		<0.001	<0.001	<0.001

[a]Conditional logistic regression adjusted for time-varying covariates (i.e. age, congestive heart failure, hypertension, diuretic use and serum creatinine levels). [b]Conditional logistic regression further adjusted for time-varying alcohol intake and dietary factors (i.e. intakes of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre). Further adjustment of baseline covariates (i.e. weight, race and education level) did not change these multivariate OR estimates as these time-fixed variables are implicitly adjusted by these models (see text for details).

beneficial effect in achieving this therapeutic goal was also evident among those with gout, this finding is likely generalizable to individuals with existing gout.

Although we found considerable odds of achieving the popular therapeutic serum urate goal associated with weight loss in the current study, the observed serum urate differences appeared less impressive, compared with those achieved by typical urate-lowering agents. This appears to support for the rationale for pharmacological urate-lowering strategies in gout with frequent flares, tophaceous gout or substantial urate load with higher levels of serum urate. Nevertheless, our data suggest that among men with a high cardiovascular risk profile and more moderate level of hyperuricaemia, losing weight sizeably increases the odds of achieving the widely accepted therapeutic goal of serum urate level. Furthermore, weight reduction can also be offered to the patients (with modestly elevated serum urate levels) as an alternative to avoid the need of indefinite serum urate-lowering medication.

Weight loss likely decreases uric acid levels by increasing renal excretion of urate and in part by decreasing urate production [39–41]. For example, an intervention study of 27 obese individuals found that fractional excretion of uric acid was significantly reduced (4% in men and 5% in women as compared with 11 and 12% in normal controls, respectively) [14]. Interestingly, urinary urate excretions were also lower in obese subjects than in controls, suggesting that hyperuricaemia in these obese individuals was mainly attributed to an impaired renal clearance of uric acid rather than overproduction. Furthermore, weight reduction by low calorie diet and exercise therapy resulted in the normalization of fractional excretion of uric acid [14]. This is likely through decreasing insulin resistance and insulin levels, which lead to decreased renal excretion of urate and hyperuricaemia. For example, exogenous insulin has been shown to reduce the renal excretion of urate in both healthy and hypertensive subjects [42–44]. Renal clearance of urate has been shown to have an inverse relation with both the degree of insulin

TABLE 5 Multivariable ORs[a] of achieving serum urate levels ≤60 μmol/l according to subgroup characteristics

| | Weight change from baseline, kg | | | | | | | |
| | Loss | | | No change (−0.9 to 0.9) | Gain | | | P-value for trend |
	≥10	5–9.9	1–4.9		1–4.9	5–9.9	≥10	
Age, years								
<47	3.86 (3.09, 4.83)	2.20 (1.91, 2.54)	1.42 (1.28, 1.57)	1.0 (Referent)	0.72 (0.64, 0.80)	0.39 (0.33, 0.46)	0.36 (0.26, 0.48)	<0.001
≥47	3.96 (3.09, 5.07)	2.13 (1.83, 2.48)	1.45 (1.30, 1.62)	1.0 (Referent)	0.81 (0.72, 0.91)	0.49 (0.39, 0.60)	0.32 (0.21, 0.51)	<0.001
Race								
Caucasian	3.98 (3.36, 4.72)	2.27 (2.04, 2.53)	1.49 (1.38, 1.60)	1.0 (Referent)	0.75 (0.69, 0.82)	0.43 (0.38, 0.49)	0.34 (0.26, 0.44)	<0.001
African American	3.34 (1.59, 7.03)	1.23 (0.84, 1.80)	0.94 (0.72, 1.23)	1.0 (Referent)	0.81 (0.60, 1.09)	0.40 (0.25, 0.66)	0.50 (0.19, 1.30)	<0.001
Education								
≤12 Grade	3.07 (2.35, 4.00)	2.00 (1.69, 2.37)	1.33 (1.18, 1.51)	1.0 (Referent)	0.78 (0.68, 0.89)	0.42 (0.34, 0.52)	0.33 (0.22, 0.51)	<0.001
>12 Grade	4.54 (3.67, 5.62)	2.27 (1.99, 2.59)	1.49 (1.36, 1.64)	1.0 (Referent)	0.74 (0.67, 0.82)	0.43 (0.37, 0.51)	0.36 (0.27, 0.49)	<0.001
Gout								
No	4.02 (3.36, 4.81)	2.14 (1.92, 2.40)	1.42 (1.31, 1.53)	1.0 (Referent)	0.73 (0.67, 0.79)	0.40 (0.35, 0.46)	0.30 (0.23, 0.40)	<0.001
Yes	3.19 (1.99, 5.09)	2.33 (1.75, 3.11)	1.53 (1.24, 1.89)	1.0 (Referent)	1.01 (0.80, 1.27)	0.65 (0.45, 0.95)	0.58 (0.31, 1.08)	<0.001
Hypertension								
No	5.06 (3.50, 7.31)	2.29 (1.86, 2.82)	1.42 (1.24, 1.64)	1.0 (Referent)	0.69 (0.59, 0.79)	0.33 (0.26, 0.41)	0.21 (0.14, 0.33)	<0.001
Yes	3.66 (3.04, 4.42)	2.13 (1.89, 2.40)	1.43 (1.32, 1.56)	1.0 (Referent)	0.78 (0.71, 0.86)	0.49 (0.41, 0.57)	0.45 (0.33, 0.61)	<0.001
Diuretic use								
No	4.07 (3.40, 4.87)	2.26 (2.02, 2.53)	1.49 (1.37, 1.61)	1.0 (Referent)	0.75 (0.69, 0.82)	0.39 (0.34, 0.45)	0.30 (0.23, 0.40)	<0.001
Yes	3.46 (2.21, 5.41)	1.84 (1.40, 2.42)	1.25 (1.04, 1.51)	1.0 (Referent)	0.81 (0.66, 0.98)	0.69 (0.50, 0.94)	0.72 (0.40, 1.31)	<0.001
GFR (ml/min/1.73 m^2)								
≤60	9.12 (3.29, 25.2)	3.16 (1.79, 5.59)	1.94 (1.26, 2.98)	1.0 (Referent)	1.08 (0.69, 1.71)	1.11 (0.52, 2.37)	0.73 (0.19, 2.76)	<0.001
>60	3.82 (3.23, 4.52)	2.14 (1.93, 2.38)	1.43 (1.32, 1.54)	1.0 (Referent)	0.75 (0.69, 0.81)	0.42 (0.36, 0.48)	0.35 (0.27, 0.44)	<0.001
Alcohol intake								
No	3.38 (1.88, 6.08)	2.59 (1.78, 3.79)	1.86 (1.41, 2.45)	1.0 (Referent)	0.87 (0.65, 1.15)	0.57 (0.37, 0.89)	0.43 (0.19, 0.98)	<0.001
Yes	3.96 (3.33, 4.70)	2.13 (1.91, 2.38)	1.40 (1.30, 1.52)	1.0 (Referent)	0.75 (0.69, 0.81)	0.42 (0.36, 0.48)	0.35 (0.27, 0.45)	<0.001
Intervention group								
Special intervention	3.65 (2.96, 4.50)	1.99 (1.74, 2.28)	1.35 (1.22, 1.50)	1.0 (Referent)	0.80 (0.72, 0.90)	0.47 (0.39, 0.56)	0.42 (0.30, 0.59)	<0.001
Usual care	4.36 (3.31, 5.75)	2.48 (2.09, 2.94)	1.54 (1.38, 1.72)	1.0 (Referent)	0.72 (0.64, 0.80)	0.39 (0.33, 0.48)	0.30 (0.21, 0.43)	<0.001
BMI, kg/m^2								
<25	2.91 (1.25, 6.75)	2.28 (1.73, 2.99)	1.28 (1.09, 1.49)	1.0 (Referent)	0.67 (0.58, 0.79)	0.32 (0.24, 0.41)	0.25 (0.15, 0.42)	<0.001
25–29.9	4.19 (3.30, 5.31)	2.12 (1.84, 2.43)	1.47 (1.33, 1.62)	1.0 (Referent)	0.77 (0.69, 0.86)	0.47 (0.39, 0.56)	0.32 (0.22, 0.46)	<0.001
≥30	3.64 (2.83, 4.70)	2.23 (1.83, 2.73)	1.54 (1.31, 1.82)	1.0 (Referent)	0.85 (0.71, 1.02)	0.48 (0.37, 0.64)	0.48 (0.31, 0.75)	<0.001

[a]Conditional logistic regression adjusted for time-varying covariates [i.e. age, congestive heart failure, hypertension, diuretic use, serum creatinine levels, alcohol intake and dietary factors (intakes of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre)].

resistance [45] and visceral fat area, as measured by abdominal CT [46]. Insulin may enhance renal urate reabsorption via stimulation of urate-anion exchanger URAT1 [47] and/or the Na^+-dependent anion co-transporter in brush border membranes of the renal proximal tubule [2]. Additionally, since serum levels of leptin and urate tend to rise together [48, 49], some investigators have suggested that leptin may affect renal reabsorption [2]. Finally, in the insulin resistance syndrome, impaired oxidative phosphorylation may increase systemic adenosine concentrations by increasing the intracellular levels of coenzyme A esters of long-chain fatty acids [2]. Increased adenosine, in turn, can result in renal retention of sodium, urate and water [50–53]. Some have speculated that chronically increased extracellular adenosine concentrations may also contribute to hyperuricaemia by increasing urate production [50].

Several strengths and potential limitations of our study deserve comment. Our analyses included a large number of longitudinal observations (78 881 visits from 12 379 men) and provided overall precise estimates based on multiple time-points, as well as relevant subgroup-specific data, including those with gout. Our person-specific analyses tend to have more clinically relevant interpretations of the effect of weight change on the change in serum urate levels for a given individual. Furthermore, in these person-specific analyses (conditioned on each cohort participant), potential confounders that vary between individuals, including unmeasured ones, become irrelevant, as one visit in a given person is compared with another visit within the same person. Relevant time-varying covariates were prospectively collected and adjusted for in our study, including blood pressure, diuretic use, renal function, alcohol intake and congestive heart failure. Nutritional data in MRFIT were collected on one 24-h dietary recall per visit, which were of limited reliability [30]. Thus, adjusting for these dietary variables in our multivariate analysis may not have been effective. The MRFIT study was a randomized trial that evaluated intervention of multiple risk factors, including weight reduction attempts among overweight and obese individuals, but some interventions were irrelevant or even contributed to hyperuricaemia (e.g. pharmacological intervention for hypertension using hydrochlorothiazide or chlorthalidone), precluding a simple comparison between the trial groups for the outcome of serum urate level. Nevertheless, the closely consistent results between the trial assignment groups were reassuring. The diagnosis of gout by a physician that we used for a sub-grouping purpose was not validated in this study. Although it is unlikely that misclassification of this sub-grouping variable would explain the strong associations observed in each subgroup, confirming these results using specific case definitions of gout would be valuable. Finally, our study was observational; thus, we cannot rule out the possibility that unmeasured factors might have contributed to the observed associations.

Men in the MRFIT were at relatively high risk of developing coronary artery disease, and thus these results are most directly generalizable to men with a similar cardiovascular risk profile. Although the demographic characteristics of our study participants (i.e. men aged 35–57 years) reflects a population at a high risk for hyperuricaemia, the generalizability of our findings to men with a different demographic profile or lower cardiovascular risk remains to be studied. Furthermore, given the influence of female hormones on the risk of hyperuricaemia in women [54, 55], prospective studies of female populations would be valuable.

In conclusion, this prospective data indicate that weight reduction could help achieve a widely accepted therapeutic urate target level ($\leqslant 360\,\mu mol/l$) among men with a high cardiovascular risk profile. Weight loss of $\geqslant 10\,kg$ could lead to a nearly 4-fold increase in the odds of achieving serum urate level $\leqslant 360\,\mu mol/l$ in a given individual.

Rheumatology key messages

- Weight reduction could help achieve a widely accepted therapeutic urate target level ($\leqslant 360\,\mu mol/l$).
- Weight loss of $\geqslant 10\,kg$ is associated with a nearly 4-fold increased odds of achieving this goal.

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