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Plasma magnesium and the risk of new-onset hyperuricaemia in hypertensive patients

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Abstract

We aimed to evaluate the relationship of plasma Mg with the risk of new-onset hyperuricaemia and examine any possible effect modifiers in hypertensive patients. This is a *post hoc* analysis of the Uric acid (UA) Sub-study of the China Stroke Primary Prevention Trial (CSPPT). A total of 1685 participants were included in the present study. The main outcome was new-onset hyperuricaemia defined as a UA concentration ≥417 μmol/l in men or ≥357 μmol/l in women. The secondary outcome was a change in UA concentration defined as UA at the exit visit minus that at baseline. During a median follow-up duration of 4·3 years, new-onset hyperuricaemia occurred in 290 (17·2 %) participants. There was a significantly inverse relation of plasma Mg with the risk of new-onset hyperuricaemia (per SD increment; OR 0·85; 95 % CI 0·74, 0·99) and change in UA levels (per SD increment; β −3·96 μmol/l; 95 % CI −7·14, −0·79). Consistently, when plasma Mg was analysed as tertiles, a significantly lower risk of new-onset hyperuricaemia (OR 0·67; 95 % CI 0·48, 0·95) and less increase in UA levels (β −8·35 μmol/l; 95 % CI −16·12, −0·58) were found among participants in tertile 3 (≥885·5 μmol/l) compared with those in tertile 1 (<818·9 μmol/l). Similar trends were found in males and females. Higher plasma Mg levels were associated with a decreased risk of new-onset hyperuricaemia in hypertensive adults.

Key words: **Magnesium: Uric acid: Hyperuricaemia: Hypertensive patients**

Over the past few decades, the prevalence of hyperuricaemia has been increasing and ranged from 2·6 to 36 % in different populations[1–4]. A recent nation-wide study found that the prevalence of hyperuricaemia was up to 13·3 % in China[5]. Hyperuricaemia is a precipitating factor for gout[6] as well as a risk factor for diabetes, the metabolic syndrome and CVD[7–9]. Prior studies have demonstrated that serum uric acid (UA) levels may be affected by many factors such as age, sex, diet and race[10]. In recent years, the effects of minerals on the risk of hyperuricaemia have been the focus of scientific research[11].

Mg is the fourth most abundant mineral found in the body and is the second most common intracellular cation after K. Serum or plasma Mg is the most commonly used biomarker to assess Mg status in clinical practice[12]. It reflects not only dietary intake but also intestinal absorption, renal reabsorption and excretion, and hormone regulation[13]. It has been reported that higher plasma

Abbreviations: CSPPT, China Stroke Primary Prevention Trial; SBP, systolic blood pressure; UA, uric acid.

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British Journal of Nutrition

Mg or Mg intake may be related to a lower risk of diabetes[14], cancer[15], chronic kidney disease[16] and cardiac death[17]. Furthermore, although some cross-sectional studies found that Mg from blood or dietary intake was inversely associated with the prevalence of hyperuricaemia[18–20], few studies have been conducted to investigate the prospective relationship of Mg concentrations from blood with new-onset hyperuricaemia.

Therefore, our present study, a *post hoc* analysis of the UA Sub-study of the China Stroke Primary Prevention Trial (CSPPT)[21], aimed to evaluate the prospective association between plasma Mg and risk of new-onset hyperuricaemia and examine any possible effect modifiers among hypertensive patients.

Methods

Study participants and design

The sample population for this study was drawn from the UA sub-study of the CSPPT. The study design and major results of the CSPPT (clinicaltrials.gov; NCT00794885)[21,22] and the UA sub-study of the CSPPT[23] have been described in detail previously. Briefly, the CSPPT was a multi-community, randomised, double-blind, controlled trial conducted from 19 May 2008 to 24 August 2013 in thirty-two communities in China. Eligible participants were men and women aged 45–75 years with hypertension, defined as seated resting systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure ≥90 mmHg at both the screening and recruitment visit or who were taking antihypertensive medication. The major exclusion criteria included history of physician-diagnosed stroke, myocardial infarction, heart failure, post-coronary revascularisation, and/or congenital heart disease.

The UA Sub-study enrolled CSPPT participants from twenty communities in Jiangsu province excluding those individuals who were taking UA-lowering medication or who had missing UA concentrations at baseline.

Intervention and follow-up. In the CSPPT, a total of 20 702 eligible participants were randomly assigned, in a 1:1 ratio, to one of the two treatment groups: a daily oral dose of one tablet containing 10 mg enalapril and 0·8 mg folic acid (the enalapril–folic acid group), or a daily oral dose of one tablet containing 10 mg enalapril only (the enalapril-only group). Participants were followed up every 3 months. Before the study ended, an exit visit was conducted for blood sample collection and assessment of hyperuricaemia outcomes.

Selection samples from the China Stroke Primary Prevention Trial. Mg deficiencies have been associated with cancer, CVD and mortality[15,17]. Therefore, we selected two cohorts of study participants from the CSPPT. Study 1 included 1326 incident stroke, cancer or all-cause mortality cases matched with 1264 corresponding controls. Controls were randomly chosen from the remaining participants who did not develop the corresponding end points during the follow-up. Controls were matched with the cases on a 1:1 ratio for age (no more than 1 year), sex, treatment group and study site. Study 2 included 1500 subjects randomly selected from the CSPPT. A total of 196 participants were included both in study1 and study 2. The present analysis utilised data from study 1 and study 2; therefore, participants had a wide range of baseline Mg levels, and the analysis had enough power to examine the relation of plasma Mg with new-onset hyperuricaemia.

The total study sample for the present study included participants from the study 1 and study 2 in the UA sub-study with plasma Mg measurements at baseline, as well as complete data on UA at both the baseline and exit visits, and who were free of hyperuricaemia at baseline (online Supplementary Fig. S1). This study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China.

Outcomes

The main outcome was new-onset hyperuricaemia in participants with normal UA concentrations (<357 μmol/l) at baseline. Hyperuricaemia was defined as a UA concentration ≥417 μmol/l in men or ≥357 μmol/l in women[24].

The secondary outcome was change in UA concentrations, defined as UA concentrations at the exit visit minus that at baseline.

Laboratory assays

Blood samples of all participants were collected at both the baseline and the exit visit. Serum folate was measured by a commercial laboratory using a chemiluminescent immunoassay (New Industrial). Serum concentrations of UA, total homocysteine, lipids and fasting glucose were measured with the use of automated analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. Plasma Mg was measured by inductively coupled plasma mass spectrometry in a commercial laboratory (Beijing DIAN Medical Laboratory, China). Both intra-assay and inter-assay CV of duplicate samples (randomly placed among the study samples) were calculated. The intra-assay CV of Mg ranged from 0·78 to 5·20 %, while the inter-assay CV of Mg was 4·78 %. The estimated glomerular filtration rate was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation[25].

Statistical analysis

To maximum study power, we combined study 1 and study 2 for the present analysis (online Supplementary Fig. S1). Furthermore, as a sensitivity analysis, we also evaluated the relation of plasma Mg with new-onset hyperuricaemia in study 1, study 2 and in participants without incident stroke, cancer or all-cause mortality during follow-up period, respectively.

Baseline characteristics are presented as mean (SD) for continuous variables and proportions for categorical variables. Differences in baseline characteristics by Mg tertiles were compared using ANOVA tests, or χ^2 tests, accordingly.

Multivariable logistic regression models and linear regression models were used to examine the relationship of baseline plasma Mg with new-onset hyperuricaemia and the change in UA concentrations, respectively, without and with adjustment for age, sex, BMI, UA, fasting glucose, total cholesterol, TAG, total homocysteine, folate, estimated glomerular filtration rate,

Table 1. Baseline characteristics of study participants by magnesium tertiles (T1–T3) (Mean values and standard deviations; numbers and percentages)

			Mg (μmol/l)						
	Overall (*n* 1685)		T1 (<818·9) (*n* 562)		T2 (818·9–<885·5) (*n* 561)		T3 (≥885·5) (*n* 562)		
Characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*
Age (years)	60·6	7·6	60	7·8	60·6	7·6	61·1	7·3	0·038
Male									0·263
n	615		205		218		192		
%	36·5		36·5		38·9		34·2		
BMI (kg/m^2)	25·4	3·5	25·1	3·4	25·5	3·6	25·6	3·6	0·042
Current smoking									0·260
n	384		128		144		112		
%	22·8		22·8		25·7		19·9		
Current alcohol drinking									0·199
n	349		111		133		105		
%	20·7		19·8		23·8		18·7		
BP (mmHg)									
Baseline SBP	170	21·6	170·6	22·4	169·3	21·2	170·2	21	0·589
Baseline DBP	94·7	12·2	94·2	12·3	94·7	12·6	95·2	11·7	0·363
Time-averaged SBP	140·2	10·9	140·4	10·8	140·2	11·2	139·9	10·6	0·716
Time-averaged DBP	83·2	7·3	83	7·6	83·2	7·4	83·3	6·9	0·853
Laboratory results									
Total cholesterol (mmol/l)	5·7	1·1	5·7	1·2	5·7	1·1	5·8	1·1	0·112
TAG (mmol/l)	1·6	0·9	1·6	1·0	1·6	0·8	1·7	0·9	0·054
Folate (ng/ml)	7·7	3·4	8·2	3·5	7·6	3·2	7·4	3·4	<0·001
Fasting glucose (mmol/l)	6·1	2·0	6·6	2·7	6·0	1·7	5·8	1·3	<0·001
Total homocysteine (μmol/l)	14·8	9·3	14·6	10·3	15·1	9·2	14·8	8·2	0·594
Vitamin B_{12} (pg/ml)	410·4	167·5	422·4	187·1	404·8	156·3	404·1	156·7	0·118
eGFR (ml/min per 1·73 m^2)	94·0	11·9	95·6	12·5	93·5	11·4	93·1	11·7	<0·001
UA (μmol/l)	267·4	51·5	262·4	52·5	269·1	53·3	270·6	48·1	0·017
Medication use									
Antihypertensive drugs									0·573
n	817		263		280		274		
%	48·5		46·8		49·9		48·8		
Lipid-lowing drugs									0·668
n	10		2		4		4		
%	0·6		0·4		0·7		0·7		
Glucose-lowing drugs									0·004
n	38		22		10		6		
%	2·3		3·9		1·8		1·1		
Anti-platelet drugs									0·071
n	64		13		24		27		
%	3·8		2·3		4·3		4·8		

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; UA, uric acid.

SBP, smoking and drinking status at baseline, treatment group and mean SBP during the treatment period. We used cubic B-spline with four knots (5th (725·1 μmol/l), 35th (823·2 μmol/l), 65th (881·9 μmol/l) and 95th (992·3 μmol/l) percentiles of baseline plasma Mg) to model the relation between plasma Mg and new-onset hyperuricaemia by the R package *spline*[26]. The middle point of first tertile for baseline plasma Mg (777·3 μmol/l) was selected as an anchor point. Non-linearity of the relationship of plasma Mg and new-onset hyperuricaemia was tested using a likelihood ratio test comparing two multivariable logistic regression models: one including only linear effect and second including also quadratic and cubic terms[27]. As additional exploratory analyses, possible modifications of the association between plasma Mg and new-onset hyperuricaemia were also assessed for above listed covariables.

A two-tailed $P < 0·05$ was considered to be statistically significant in all analyses. R software, version 3.3.2 (http://www.R-project.org/) was used for all statistical analyses.

Results

Study participants and baseline characteristics

As illustrated in the flow chart (online Supplementary Fig. S1), a total of 1685 participants were included in the final analysis. Baseline characteristics of the participants are presented by plasma Mg tertiles in Table 1. Plasma Mg levels were positively associated with age and BMI and were inversely associated with folate, fasting glucose, estimated glomerular filtration rate and glucose-lowering drugs.

Association between plasma magnesium and study outcomes

During the median follow-up duration of 4·3 years (interquartile range: 4·2–4·6 years), new-onset hyperuricaemia occurred in 290 (17·2 %) participants. Overall, no significant curvilinear association was observed between Mg and new-onset

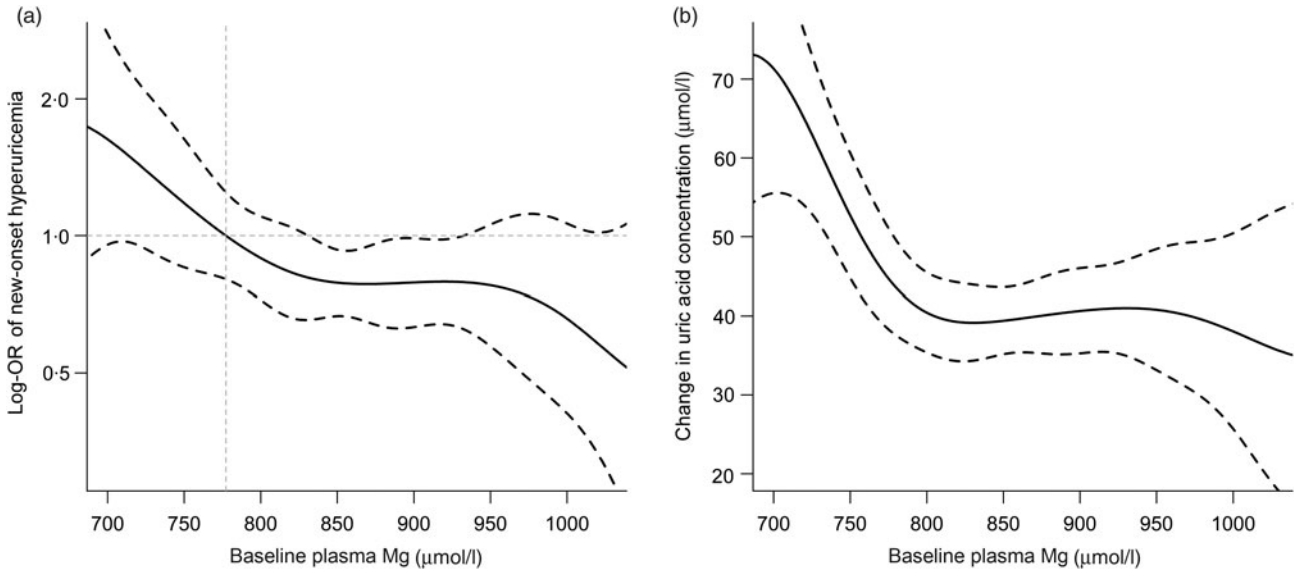

Fig. 1. Relationship of plasma magnesium with new-onset hyperuricaemia (a) and change in uric acid concentration (b) in hypertensive patients*. *Adjusted for age, sex, BMI, uric acid, fasting glucose, total cholesterol, TAG, total homocysteine, folate, estimated glomerular filtration rate, systolic blood pressure (SBP), smoking and drinking status at baseline, treatment group and mean SBP during the treatment period. The middle point of first tertile for baseline plasma magnesium (777·3 μmol/l) was selected as an anchor point.

hyperuricaemia ($P_{\text{for non-linearity}} = 0{\cdot}436$). The linear dose–response analysis suggested that per SD increment of plasma Mg was associated with 15 % reduction in new-onset hyperuricaemia (OR 0·85; 95 % CI 0·74, 0·99) (Fig. 1(a)). Consistently, there was a significantly inverse relationship of plasma Mg with the change in UA levels (per SD increment; β −3·96 μmol/l; 95 % CI −7·14, −0·79) (Fig. 1(b)).

When plasma Mg was analysed as tertiles, a significantly lower risk of new-onset hyperuricaemia (OR 0·67; 95 % CI 0·48, 0·95) and less increase in UA levels (β −8·35 μmol/l; 95 % CI −16·12, −0·58) were found among participants in tertile 3 (≥885·5 μmol/l) compared with those in tertile 1 (<818·9 μmol/l) (Tables 2 and 3). Similar trends were found in males and females (Tables 2 and 3), in participants without

Table 2. Association between plasma magnesium and new-onset hyperuricaemia (Numbers and percentages; odds ratios and 95 % confidence intervals)

			Model 1*			Model 2†		
Mg (μmol/l)	Events/*n*	%	OR	95 % CI	*P*	OR	95 % CI	*P*
Total population								
Per SD increment	290/1685	17·2	0·86	0·75, 0·98	0·028	0·85	0·74, 0·99	0·032
Tertiles								
T1 (<818·9)	103/562	18·3	Ref.			Ref.		
T2 (818·9–<885·5)	96/561	17·1	0·78	0·57, 1·09	0·144	0·74	0·53, 1·05	0·089
T3 (≥885·5)	91/562	16·2	0·70	0·51, 0·98	0·036	0·67	0·48, 0·95	0·026
$P_{\text{for trend}}$			0·036			0·027		
Males								
Per SD increment	76/615	12·4	0·84	0·66, 1·07	0·159	0·81	0·62, 1·05	0·114
Tertiles								
T1 (<819·1)	34/205	16·6	Ref.			Ref.		
T2 (819·1–<881·0)	22/205	10·7	0·60	0·34, 1·09	0·092	0·53	0·28, 1·00	0·049
T3 (≥881·0)	20/205	9·8	0·53	0·29, 0·96	0·036	0·45	0·23, 0·86	0·016
$P_{\text{for trend}}$			0·032			0·015		
Females								
Per SD increment	214/1070	20·0	0·86	0·72, 1·02	0·077	0·84	0·70, 1·01	0·060
Tertiles								
T1 (<818·2)	69/357	19·3	Ref.			Ref.		
T2 (818·2–<887·6)	75/356	21·1	0·88	0·59, 1·30	0·512	0·84	0·56, 1·28	0·421
T3 (≥887·6)	70/357	19·6	0·78	0·53, 1·17	0·229	0·76	0·50, 1·17	0·216
$P_{\text{for trend}}$			0·230			0·218		

Ref., reference; UA, uric acid; SBP, systolic blood pressure.
* Adjusted for age, sex and UA at baseline.
† Adjusted for age, sex, BMI, UA, fasting glucose, total cholesterol, TAG, total homocysteine, folate, estimated glomerular filtration rate, SBP, smoking and drinking status at baseline, treatment group, and mean SBP during the treatment period.

British Journal of Nutrition

Table 3. Association between plasma magnesium and change in uric acid (UA) concentrations (Mean values and standard deviations; β-coefficients and 95 % confidence intervals)

	UA change (μmol/l)		Model 1*			Model 2†		
Mg (μmol/l)	Mean	SD	β	95 % CI	*P*	β	95 % CI	*P*
Total population								
Per SD increment	44·2	67·9	−3·89	−7·02, −0·75	0·015	−3·96	−7·14, −0·79	0·014
Tertiles								
T1 (<818·9)	51·0	69·5	Ref.			Ref.		
T2 (818·9–<885·5)	41·4	70·7	−7·95	−15·61, −0·30	0·042	−8·09	−15·76, −0·43	0·039
T3 (≥885·5)	40·1	62·7	−8·05	−15·72, −0·37	0·040	−8·35	−16·12, −0·58	0·035
$P_{for\ trend}$			0·040			0·036		
Males								
Per SD increment	49·2	72·9	−4·57	−10·14, 1·00	0·109	−5·40	−11·20, 0·40	0·068
Tertiles								
T1 (<819·1)	56·8	77·8	Ref.			Ref.		
T2 (819·1–<881·0)	44·5	73·1	−14·01	−27·63, −0·38	0·044	−15·98	−29·92, −2·04	0·025
T3 (≥881·0)	46·3	67·1	−9·53	−23·14, 4·08	0·171	−11·11	−25·16, 2·95	0·122
$P_{for\ trend}$			0·171			0·132		
Females								
Per SD increment	41·3	64·7	−3·64	−7·40, 0·13	0·059	−3·68	−7·49, 0·14	0·059
Tertiles								
T1 (<818·2)	47·6	64·1	Ref.			Ref.		
T2 (818·2–<887·6)	39·6	69·4	−4·90	−14·11, 4·32	0·298	−4·67	−13·91, 4·57	0·322
T3 (≥887·6)	36·6	59·7	−7·93	−17·18, 1·32	0·093	−7·51	−16·90, 1·89	0·118
$P_{for\ trend}$			0·093			0·118		

Ref., reference; SBP, systolic blood pressure.
* Adjusted for age, sex and UA at baseline.
† Adjusted for age, sex, BMI, UA, fasting glucose, total cholesterol, TAG, total homocysteine, folate, estimated glomerular filtration rate, SBP, smoking and drinking status at baseline, treatment group, and mean SBP during the treatment period.

incident stroke, cancer or all-cause mortality (online Supplementary Table S1), in study 1 or 2 (online Supplementary Tables S2 and S3) and in the enalapril-only group (online Supplementary Table S4). Moreover, taking into account possible residual confounding, we further explored the association between plasma Mg and new-onset hyperuricaemia with a sequential modelling approach (online Supplementary Table S5). In the models, all the results did not change essentially.

In addition, during the treatment period, participants with higher plasma Mg levels had lower frequency use of glucose-lowering drugs (online Supplementary Table S6). However, further adjustment for the use of glucose-lowering drugs did not substantially change the results (online Supplementary Table S7).

Stratified analyses by potential effect modifiers

Stratified analyses were performed to assess the effect of Mg (Per SD increment) on the primary outcome in various subgroups (Fig. 2). None of the variables, including sex, age (<60 *v.* ≥60 years), current alcohol drinking (no *v.* yes), treatment group (enalapril-only *v.* enalapril + folic acid), SBP (<160 *v.* ≥160 mmHg), UA (<269 (median) *v.* ≥269 μmol/l), TAG (<1·4 (median) *v.* ≥1·4 mmol/l)), fasting glucose (<7·0 *v.* ≥7·0 mmol/l or diabetes), folate (<7·3 (median) *v.* ≥7·3 ng/ml), estimated glomerular filtration rate (<90 *v.* ≥90 ml/min/1·73 m^2) levels at baseline, as well as mean SBP (<140 *v.* ≥140 mmHg), stroke occurrence (no *v.* yes), and cancer occurrence (no *v.* yes) over the trial period, significantly modified the association between plasma Mg and the risk of hyperuricaemia ($P_{for\ all\ interactions}$ >0·05) (Fig. 2). Of note, at the existing sample size, the power for detecting a moderate interaction is limited; therefore, a negative finding would not necessarily confirm the absence of interaction.

Discussion

Our present study is the first to demonstrate that plasma Mg levels were inversely associated with incidence of new-onset hyperuricaemia and the magnitude of the increase in UA concentrations among general hypertensive patients.

Our findings are consistent with the published cross-sectional studies on this topic. In a Chinese population of adults over age 40 years (*n* 2904), serum Mg was inversely associated with the prevalence of hyperuricaemia in men, but not in women[18]. Wang *et al.*[19] reported that the relative odds of the overall prevalence of hyperuricaemia decreased in the fourth quintile of Mg intake (OR 0·57; 95 % CI 0·35, 0·94) and in the fifth quintile (OR 0·55, 95 % CI 0·30, 1·01) compared with the lowest quintile ($P_{for\ trend}$ = 0·091) among 5168 subjects. In addition, this association remained valid for males but not for females. Consistently, Zhang *et al.*[20] indicated that increased Mg intake was associated with decreased prevalence of hyperuricaemia in adults from the USA.

With a prospective design, our present study provides some new insights in this field. We found higher Mg levels were associated with lower risk of new-onset hyperuricaemia and less increase in UA concentrations over a median follow-up duration of 4·3 years. Mg is one of the most important dietary nutrients for humans. It is involved in a wide range of biochemical reactions, particularly, intracellular transphosphorylation, which is critical

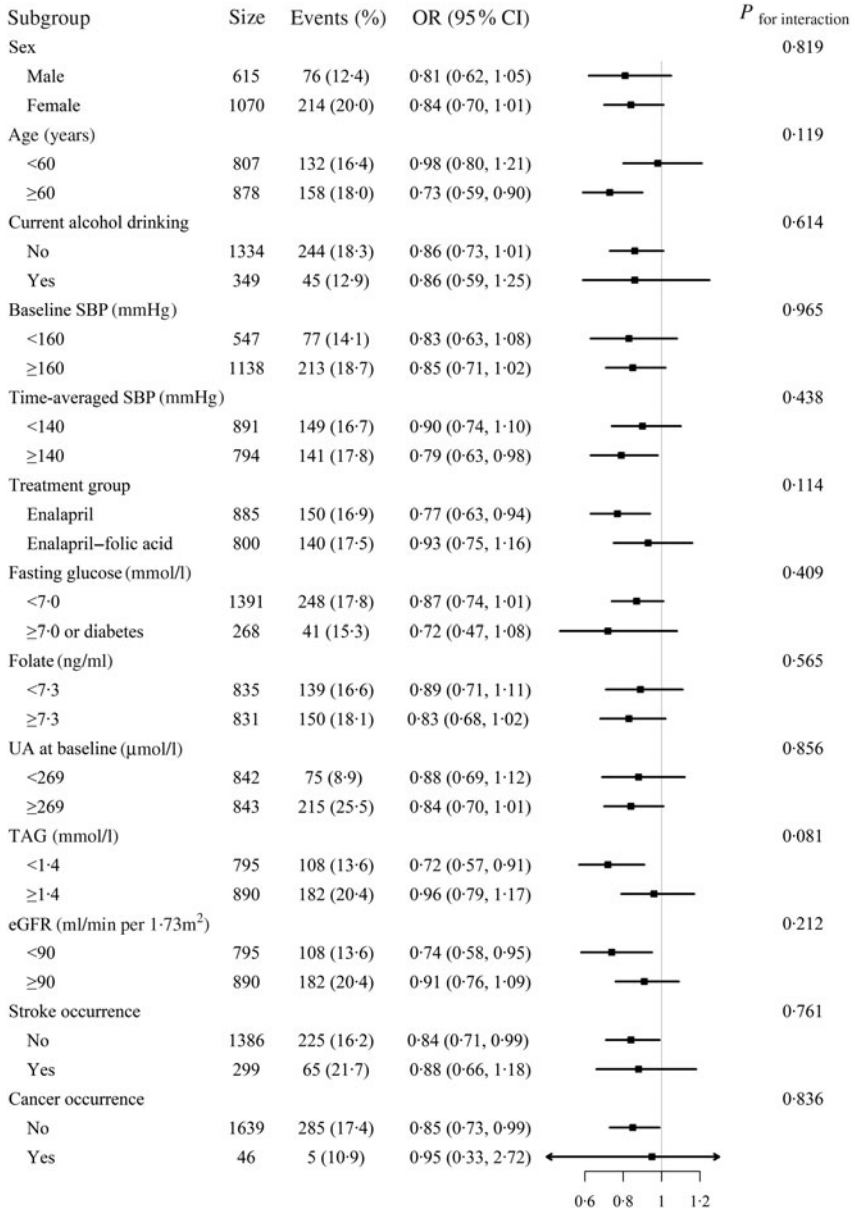

Fig. 2. Stratified analyses by potential effect modifiers for new-onset hyperuricaemia*. *Adjusted, if not stratified, for age, sex, BMI, uric acid (UA) at baseline, fasting glucose, total cholesterol, TAG, total homocysteine, folate, estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), smoking and drinking status at baseline, treatment group and mean SBP during the treatment period. Diabetes was defined as self-reported physician-diagnosed diabetes or the use of glucose-lowering drugs at baseline. Boxes denote odds ratios; lines represent 95 % confidence intervals.

for the initiation of DNA synthesis and multiplication in cultured cells[28,29]. Furthermore, low Mg levels can influence oxidative stress, consequent oxidative DNA modification and DNA repair[30], and therefore, may induce marked DNA damage and release purine nucleotides. Catabolism of the purine nucleotides ultimately leads to the production of UA. Moreover, Mg deficiency is related to an increase in C-reactive protein, IL-6 and fibrinogen, which are sensitive biomarkers of inflammation[31–33]. Additionally, a positive relationship between serum UA with IL-6 and TNF-α has been reported[34,35]. While more mechanistic studies are required, available evidence lent support for a biological plausibility of our findings.

Our analyses considered a number of potentially confounding factors, including baseline BMI, UA, fasting glucose, lipids, total homocysteine, folate, etc. Furthermore, we have evaluated possible modifications of the association between plasma Mg and new-onset hyperuricaemia for above-listed covariables. However, limitations of the present study should also be noted. First, our present study was conducted in hypertensive patients; thus, the generalisability of the results to adults without hypertension remains to be further examined. However, blood pressure measurements at both baseline and during the trial period did not significantly modify the association between plasma Mg and new-onset hyperuricaemia. Second,

Mg concentrations were only measured at baseline, which may or may not represent the Mg concentrations over the period of follow-up. Third, although adjustments were made for a broad set of covariates, residual confounding from unmeasured or incompletely measured factors cannot be excluded. Finally, a relationship between a nutrition biochemical marker may not necessarily mean that the nutrient itself is really involved. Although plasma Mg is highly associated with Mg-rich foods, the effect of Mg intake is difficult to be distinguished from the concomitant many other beneficial components. Moreover, we did not have detailed food intake information. As such, we could not examine the possible effect of Mg intake on new-onset hyperuricaemia. Overall, our results were just hypothesis generating. More clinical studies are needed to confirm our findings and explore the underlying mechanisms.

In conclusion, higher baseline plasma Mg concentrations were associated with significantly decreased risk of new-onset hyperuricaemia in hypertensive adults. If further confirmed by future studies, maintaining higher Mg concentrations may be considered as an adjuvant nutritional strategy for the prevention and treatment of hyperuricaemia.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114520001099

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