

BMJ Open Relationship between dietary magnesium intake and rheumatoid arthritis in US women: a cross-sectional study

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To cite: Hu C, Zhu F, Liu L, *et al.* Relationship between dietary magnesium intake and rheumatoid arthritis in US women: a cross-sectional study. *BMJ Open* 2020;**10**:e039640. doi:10.1136/bmjopen-2020-039640

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-039640>).

Received 22 April 2020

Revised 25 August 2020

Accepted 07 October 2020



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ABSTRACT

Objectives Diet has been shown to be associated with rheumatoid arthritis (RA), and magnesium has been shown to inhibit inflammatory responses, but research on the relationship between dietary magnesium and RA is limited and controversial. In this study, we aimed to explore the non-linear relationship between dietary magnesium intake and RA in US women.

Design Cross-sectional survey.

Setting National Health and Nutrition Examination Survey (NHANES).

Primary and secondary outcome measures Non-linear relationship between dietary magnesium intake and prevalence of RA.

Participants A total of 13 324 women aged 18–80 years (RA n=12 306, non-RA n=1018) were included in this study.

Results Overall, the absolute risk (AR) of RA was 7.24% in all participants. In the multivariable logistic regression analysis, we found a negative correlation between dietary magnesium intake and RA (OR=0.84, 95% CI 0.75 to 0.95, p=0.006). When we converted dietary magnesium intake into a categorical variable (tertiles), the ARs of the low group, the middle group and the high group were 9%, 7.1% and 4.9%, respectively. We noticed that the ORs between the three groups were not equidistant; then, we detected a U-shaped linking by smooth curve fitting and obtained inflection points at 181 and 446 mg/day. The prevalence of RA decreased when dietary magnesium intake was <181 mg/day (OR=0.7, 95% CI 0.5 to 0.8, p<0.001) and increased when it was >446 mg/day (OR=2.8, 95% CI 1.2 to 6.6, p=0.020), remaining at a minimum when it was between 181 and 446 mg/day (OR=1.0, 95% CI 0.7 to 1.2, p=0.700).

Conclusion There was a U-shaped relationship between dietary magnesium and RA in women, and our study highlights the importance of moderate dietary magnesium intake in possibly exerting a protective role in women with RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease characterised by persistent synovitis, systemic inflammation and progressive joint disability,¹ and it has been ranked as a high contributor to global disability.²

Strengths and limitations of this study

- Large, nationally representative dataset and rigorous research methods of the National Health and Nutrition Examination Survey database.
- We explored a U-shaped relationship between dietary magnesium and rheumatoid arthritis (RA) for the first time and obtained a reasonable range of dietary magnesium intake.
- The limitations of this study are that our data were derived from cross-sectional studies, and the relationship is not necessarily identified as causal.
- Some of the data in this study were from self-reports, which may result in recall bias.

RA occurs in 0.5%–1% of adults worldwide,³ yet it is more prevalent in women: before 50 years of age, the ratio of women/men affected is more than 4 and less than 2 after 60 years old.⁴ Furthermore, the disease progression and activity of RA in women is generally more severe than in men.⁵ The high incidence, high disability, substantial fiscal impact and potentially increasing burden of RA in women make research on low-cost and readily available treatment for RA an urgent global demand.⁶

As a modifiable factor for RA, diet has raised great interest among researchers. Nearly one-quarter of RA patients with longstanding disease consider that diet had a significant effect on their symptoms, and 40% of women with RA consider diet a factor contributing to the course of disease,⁷ but the sources of information are mostly extensive lay literature, and scientific research remains scant. The micronutrient magnesium is the second-most common intracellular element in the human body.⁸ Solid evidence indicates that magnesium has a crucial regulatory role in nuclear factor kappa-B (NF-κB) activation, proinflammatory cytokine production and systemic inflammation, which have been

proven to be strongly associated with the pathogenesis of RA.^{9–10} Furthermore, other studies showed that high magnesium levels are associated with low oestrogen levels in women,^{11–12} which is well known to be linked with RA.^{13–14} Therefore, there are reasons to suspect the role of dietary magnesium intake in women with RA.

Research on the relationship between magnesium and RA is limited and controversial,^{15–18} with even fewer studies on women. According to a Pakistani study, women with RA had lower levels of magnesium in their blood, serum and hair.¹⁹ In another study, dietary magnesium intake in Iranian women was below the recommended values but was not associated with RA disease activity or serum biochemical markers.²⁰ In addition, no population-based data about this relationship in women have been reported. Due to the limited sample size and methodology, there is no powerful evidence to illustrate the association of dietary magnesium intake and RA in women.

In this study, we aimed to evaluate the non-linear association between dietary magnesium intake and RA in US women while taking into account a variety of potential confounders in a large, nationally representative sample from National Health and Nutrition Examination Survey (NHANES) (1999–2016).

METHODS

Data source

NHANES is a national cross-sectional study designed to represent the civilian, non-institutionalised US population conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. Participants were interviewed for background information by trained participants at their homes and then underwent physical and medical examinations in a specifically equipped mobile examination centre. Further details on the data collection procedure and analytical guidelines are publicly available on the NHANES website.²¹

Study population

Nine 2-year-cycle data from the continuous NHANES (1999–2016) were combined for analysis with greater statistical reliability ($n=92\,062$). We excluded men ($n=45\,336$), participants younger than 18 years ($n=19\,087$) or older than 80 years of age ($n=919$),^{22–25} participants who had been diagnosed with other forms of arthritis, participants with missing RA data ($n=3\,438$) or dietary magnesium information ($n=9\,958$), and 13 324 participants were eventually included in the analysis (figure 1).

Dietary magnesium assessment

Dietary magnesium intake data were collected using the US Department of Agriculture (USDA)'s dietary data collection instrument, the Automated Multiple Pass Method; it has been proven that the AMPM accurately measures group energy intake.²⁶ Dietary information was collected by trained dietary interviewers; participants were asked about all the food and drink they consumed

in the 24 hours before the interview, and the amount of food was estimated based on multiple measurement guides, including cups, bowls, glasses, spoons and so on. Through the US Department of Agriculture Food and Nutrient Databases for Dietary Studies, magnesium intakes could be calculated by using What's in the Foods You Eat search tool.²⁷ Because of the skewed distribution of dietary magnesium intake, we performed a log₂ transform to reduce the effect of outliers.

RA assessment

Our primary outcome was RA, which was defined as a binary variable from the medical condition questionnaire; trained interviewers went to participants' homes and used a computer-assisted personal interviewing system to ask questions. First, participants were asked, "Has a doctor ever said you had arthritis?" If he/she said 'No', the participant was defined as 'Non-RA', if the participant answered 'Yes', then he/she was asked "Which type of arthritis was it?" Options included osteoarthritis or degenerative arthritis, rheumatoid arthritis, psoriatic arthritis, other, do not know or refused to answer. Participants who did not know what type of arthritis they had or refused to answer were excluded, and those who responded 'rheumatoid arthritis' were considered 'RA'.

Covariates

Sociodemographic data were compiled from demographics and questionnaires, including sex, age, body mass index, race/ethnicity (Mexican-American, non-Hispanic white, non-Hispanic black, other), educational level (<high school, high school graduate, some college/graduate school), household income-to-poverty ratio (<1, ≥1), smoking history (defined as having smoked at least 100 cigarettes in life) and drinking history (defined as having at least 12 alcohol drinks in 1 year). Meanwhile, we

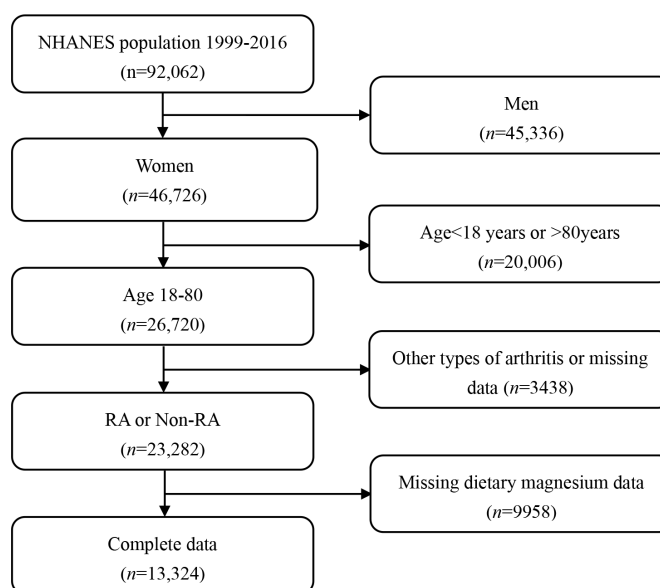


Figure 1 Flowcharts illustrating sample selection from NHANES 1999–2016. NHANES, National Health and Nutrition Examination Survey; RA, rheumatoid arthritis.

used serum cotinine to assess current smoking or second-hand smoke status (<3 , ≥ 3 ng/mL).²⁸

We also considered other chronic medical conditions from questionnaires and laboratory data as potential confounders, including hypertension, diabetes, total cholesterol and triglyceride levels.

Oral contraceptives have been reported to have a protective effect on RA in women,²⁹ so the oral contraceptive history was adjusted from the reproductive questionnaire in this study.³⁰

Statistical analysis

We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross-sectional checklist when writing our report.³¹ NHANES uses a complex, multistage probability sampling design³²; therefore, our analysis took into account the proposed weighting methodology. Weighted χ^2 tests were conducted for categorical variables, and weighted Student's *t* tests were used for continuous variables. All *p* values were from two-sided tests ($\alpha=0.05$).

Dietary magnesium intake was initially analysed as a continuous variable; then, it was ranked from low to high and categorised into tertiles to explore potential non-linear relationships. The lowest tertile (T1) was defined as the reference group. Tests for trends (P_{trend}) were performed by entering the dietary magnesium intake (tertile-categorical) as a continuous variable and rerunning the corresponding regression models. The purpose of this process was to observe whether the trend of the OR value was stable when dietary magnesium was treated as a continuous variable or as a categorical variable.

We used both weighted univariable and multivariable logistic regression models. Crude model: no covariable was adjusted; model 1: only social demographic covariables were adjusted; model 2: all covariables shown in table 1 were adjusted.

To investigate whether there was a non-linear relationship between magnesium intake and RA in women, we conducted a weighted generalised additive model (GAM) and smooth curve fitting (penalised spline method). When we detected a non-linear association, we used a recursive algorithm to calculate the inflection point; it was determined by using trial and error: selecting points along a predefined interval and then choosing the turning point that gave the maximum model likelihood.^{33 34} On both sides of the inflection point, we constructed a weighted two-piecewise linear regression model. Then, we conducted a log likelihood ratio test for the linear regression model and two-piecewise linear regression model to determine the best fit model.

Analyses in this study were performed with the statistical software package R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Boston, Massachusetts, USA).

Consent to participate

All participants provided written informed consent, and all procedures were approved by the National Center for Health Statistics Research Ethics Review Board.³⁵ These data are publicly available, so this study did not require approval from the institutional review board.

Patient and public involvement

Participants were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Baseline characteristics of the study population

The characteristics of the eligible participants are summarised in table 1. The absolute risk (AR) of RA was 7.24% in all women. Compared with the non-RA group, the RA group was more likely to be heavier, older, non-Hispanic blacks, smokers and former users of contraceptives and to have comorbidities and lower educational levels and income levels. Furthermore, dietary magnesium intake in the RA group appeared to be slightly lower than that in the non-RA group (all *p* values <0.05).

Multiple logistic regression

Table 2 shows the association between dietary magnesium intake and RA. In the crude model, we found that dietary magnesium was negatively correlated with RA (OR=0.72, 95% CI 0.66 to 0.78, $p<0.001$). Then, we adjusted for sociodemographic variables in model 1, and the correlation was slightly weaker, but the protective effect of dietary magnesium persisted (OR=0.83, 95% CI 0.75 to 0.93, $p<0.001$). In model 2, we fully adjusted for covariables including sociodemographic variables, smoking and drinking history, comorbidities and contraceptive use, and the association remained robust (OR=0.84, 95% CI 0.75 to 0.95, $p<0.01$).

Then, we converted dietary magnesium intake into a categorical variable to detect a dose-response relationship (table 2). The ARs of the lowest group, the middle group and the highest group were 9%, 7.1% and 4.9%, respectively. In the crude model, we found a monotonic decrease in RA across the dietary magnesium tertiles ($P_{\text{trend}}<0.001$); this trend robustly remained in model 1 and model 2. As we can see in the table, in model 2, the OR of RA decreased by 0.78 times in the third tertile of dietary magnesium intake compared with the first tertile (OR=0.78, 95% CI 0.63 to 0.96, $p<0.05$).

Analysis of non-linear relationship

In the multivariable logistic regression analysis, when we adjusted all continuous variables in the covariates as smooth in GAM, dietary magnesium was found to be significantly associated with RA prevalence (OR=0.84, 95% CI 0.75 to 0.95, $p<0.01$). When we converted dietary magnesium intake into tertile groups, the OR value showed non-equidistant changes, suggesting the existence of a non-linear relationship, so we conducted

Table 1 Baseline characteristics of selected participants from NHANES 1999–2016

Characteristics	RA (n=12 306)	Non-RA (n=1018)	P value
Age (years)	43.0±16.2	59.1±13.8	<0.001*
BMI (kg/m ²)	28.8±7.2	31.7±8.0	<0.001*
Triglyceride (mg/dL)	132.9±111.7	157.0±145.9	<0.001*
Total cholesterol (mg/dL)	197.6±42.1	199.6±44.1	0.162
Magnesium (mg) log2 transform	7.9±0.7	7.7±0.8	<0.001*
Race/ethnicity			<0.001*
Mexican–American	2302 (18.7%)	164 (16.1%)	
Other Hispanic	1192 (9.7%)	106 (10.4%)	
Non-Hispanic white	4962 (40.3%)	385 (37.8%)	
Non-Hispanic black	2618 (21.3%)	315 (30.9%)	
Other race	1232 (10.0%)	48 (4.7%)	
Education			<0.001*
Less than high school	2753 (22.4%)	389 (38.2%)	
High school	2610 (21.2%)	228 (22.4%)	
More than high school	6931 (56.4%)	401 (39.4%)	
Poverty–income ratio			<0.001*
<1	2556 (22.4%)	296 (31.4%)	
≥1	8847 (77.6%)	646 (68.6%)	
Over 100 cigarettes in a lifetime			<0.001*
No	8242 (67.0%)	546 (53.7%)	
Yes	4060 (33.0%)	471 (46.3%)	
Cotinine			<0.001*
<3 (ng/mL)	9283 (79.5%)	706 (73.1%)	
≥3 (ng/mL)	2396 (20.5%)	260 (26.9%)	
The consumption of at least 12 alcohol drinks in the previous year			<0.001*
No	4363 (38.6%)	457 (47.1%)	
Yes	6950 (61.4%)	514 (52.9%)	
Hypertension			<0.001*
No	8037 (74.9%)	342 (38.8%)	
Yes	2700 (25.1%)	539 (61.2%)	
Diabetes			<0.001*
No	11 388 (92.6%)	748 (73.5%)	
Yes	907 (7.4%)	270 (26.5%)	
Oral contraceptives			0.005*
No	3506 (31.1%)	344 (35.5%)	
Yes	7782 (68.9%)	626 (64.5%)	

Weighted values are means and their SD (continuous variables) or percentages (categorical variables).

*p<0.05, significantly different between two groups.

NHANES, National Health Nutrition and Examinations Survey; RA, rheumatoid arthritis; BMI, body mass index.

smooth curve fitting (penalised spline method) to detect the non-linear relationship. As shown in [figure 2](#), there was an interesting U-shaped relationship between dietary magnesium intake and RA after fully adjusting the covariates in [table 1](#). Then, we conducted a recursive algorithm to calculate the inflection point, as shown in [table 3](#): if a

woman's dietary magnesium intake (log₂) was below 7.5 (ie, <181 mg), a one-unit increase in magnesium intake (log₂) resulted in a decrease of the relative odds of RA by 0.7 times with respect to the second, reference tertile (OR=0.7, 95% CI 0.5 to 0.8, p<0.001); when magnesium intake (log₂) was between 7.5 and 8.8 (ie, 181–446 mg),

Table 2 Univariable and multivariable logistic regression of the association between magnesium intake and prevalence of RA in women

Exposure	Crude model (n=13324)	Model 1 (n=12227)	Model 2 (n=9317)	GAM(n=9317)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Magnesium (log2 transform)	0.72 (0.66 to 0.78)***	0.83 (0.75 to 0.93)***	0.90 (0.75 to 1.09)	0.84 (0.75 to 0.95)**
T1 (1.0–7.5)	Ref	Ref	Ref	Ref
T2 (7.5–8.2)	0.81 (0.70 to 0.94)**	0.86 (0.73 to 1.02)	0.90 (0.75,1.09)	0.86 (0.71 to 1.05)
T3 (8.2–11.4)	0.55 (0.47 to 0.65)***	0.76 (0.63 to 0.91)**	0.77 (0.62 to 0.94)*	0.78 (0.63 to 0.96)*
P _{trend}	<0.001	0.003	0.012	0.019

Crude model adjusted for: none.

Model 1 adjusted for: social demographic covariables.

Model 2 adjusted for: all covariates listed in [table 1](#) were adjusted.

*p<0.05; **p<0.01; ***p<0.001, significantly associated with prevalence of RA in women.

GAM, all continuous variables in the covariates were adjusted as smooth; RA, rheumatoid arthritis.

the relative odds of RA did not change as dietary magnesium intake increased (OR=1.0, 95% CI 0.7 to 1.2, p=0.7). When magnesium intake (log2) was more than 8.8 (ie, >446 mg), the relative odds of RA increased by 2.8 times for a one-unit additional intake of magnesium (log2) compared with the second, reference tertile (OR=2.8, 95% CI 1.2 to 7.2, p=0.02).

DISCUSSION

In this study, a cross-sectional analysis was applied to the NHANES (1999–2016) to assess the association between dietary magnesium intake and RA among US women (18–80 years old); through multiple logistic regression, we found that RA appeared to be negatively correlated with dietary magnesium intake, and there was a dose-response relationship. However, when we verified the

non-linear relationship through smooth curve fitting, an interesting U-shaped relationship was found: dietary magnesium intake between 181 and 446 mg/day was associated with the lowest prevalence of RA, with increasing prevalence of RA in both directions away from this range.

Prior analyses of the relationship between dietary magnesium intake and RA generally involved a small sample size and no consistent conclusions. A Pakistani case-control study indicated that there was an inverse association between magnesium level (scalp hair, serum, blood, urine) and RA.¹⁹ In addition, a cross-sectional study also showed that magnesium intake in patients with RA was significantly lower than the Recommended Dietary Allowance (RDA) (320 mg/day), and negative correlations were observed between magnesium intake and RA.¹⁵ However, other studies stated conflicting results that provided non-significant associations between magnesium intake and RA.^{36 37} On the whole, we consider that the reasons for these contradictory results may involve

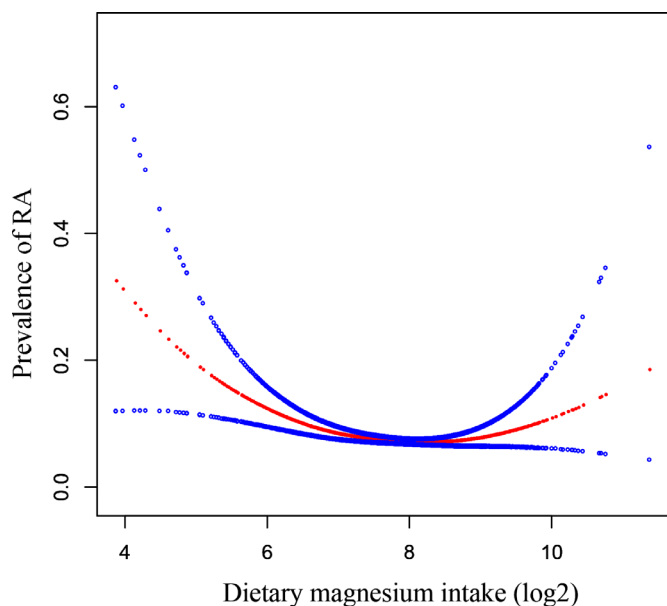


Figure 2 The non-linear correlation between dietary magnesium intake and prevalence of rheumatoid arthritis (RA) in women (using penalised spline method).

Table 3 Non-linearity addressing by weighted two-piecewise linear model in women

	Dietary magnesium intake (log2 transform)	
	OR (95% CI)	P value
Fitting by standard linear model	0.9 (0.8 to 1.0)	0.011*
Fitting by two-piecewise linear model		
<7.5	0.7 (0.5 to 0.8)	<0.001***
7.5–8.8	1.0 (0.7 to 1.2)	0.700
>8.8	2.8 (1.2 to 6.6)	0.020*
Log likelihood ratio	<0.001***	

OR has been adjusted for all covariates listed in [table 1](#).

*p<0.05; ***p<0.001, significantly associated with prevalence of RA in women.

RA, rheumatoid arthritis.

differences not only in study population, study type and sample size but also in the statistical strategy used.

Currently, there are limited studies on the association between dietary magnesium intake and RA in women, and few studies have reported insufficient dietary magnesium intake in women with RA.^{17–20} To our knowledge, this is the first study to clarify the non-linear relationship between dietary magnesium and RA in women. In this study, we used different statistical methods and found seemingly contradictory conclusions: multiple logistic regression analysis found a negative correlation between RA and dietary magnesium, but smooth curve fitting revealed a U-shaped relationship between the two. This may be due to the small sample sizes of the two subgroups with the lowest and highest dietary magnesium intake, which are easy to ignore if only third-level grouping is performed, concealing the true relationship.

Currently, different countries or regions have different RDAs of dietary magnesium for women (300–320 mg/day), and there was no specific RDA for women with RA.^{38,39} Our study explored that when dietary magnesium intake is below 181 mg/day, increased dietary magnesium intake was associated with a reduced prevalence of RA, which may be due to the anti-inflammatory effect of magnesium inhibiting proinflammatory gene expression.^{40–42} Several cross-sectional studies have reported that dietary magnesium intake is inversely associated with serum C-reactive protein (CRP),^{43–44} and oral magnesium supplementation has been shown to reduce CRP concentration in some randomised controlled trials.^{45–46} In addition, solid evidence indicates that magnesium has protective effects on articular cartilage because it reportedly enhances chondrocyte proliferation and redifferentiation as well as protects against a substantial proportion of chondrocyte damage.⁴⁷ Our research found that dietary magnesium intake was 181–446 mg/day, the relative odds of RA did not change as dietary magnesium intake increased. However, Mendelian randomisation analyses revealed that each SD increase in magnesium (0.16 mmol/L) is associated with an 8.94-fold increase in the risk of RA ($p=0.044$).¹⁸ Additionally, the joints of RA rats fed a high magnesium diet showed erosive changes in an *in vivo* experiment.¹⁵ Our results were partially consistent with those of this last study: when women's dietary magnesium intake was greater than 446 mg/day, the relative odds of RA were increased by 2.8 times for a one-unit increase in magnesium intake (\log_2) with respect to the second, reference tertile. The underlying mechanism may be the antagonism of high magnesium intake on oestrogen. This action triggers important secondary effects on RA, as oestrogen could inhibit the release of inflammatory cytokines related to RA through multiple mechanisms. Previous studies have proven that the lower serum oestrogen level among females was associated with a higher magnesium level^{11,12,48}; an oestrogen deficiency may increase the risk of RA through its effect on immune dysregulation, exacerbate inflammatory conditions and cause massive bone

destruction.^{13–14} However, due to the lack of oestrogen data in NHANES, we were unable to investigate whether oestrogen acted as an intermediate factor between dietary magnesium and RA, so more prospective studies are needed to prove this hypothesis.

As with all studies, potential limitations should be noted. First, since the research data were derived from a cross-sectional study, the relationship was not necessarily identified as causal, indicating a potential temporality bias. Second, the research participants were US women; thus, the generalisability of the findings to other populations cannot be verified. Third, part of the data in this study was self-reported, which may result in recall bias, but another study showed moderate to high levels of specificity and sensitivity in comparing self-reports to payroll data.^{49–51} Finally, due to the limitation of the NHANES, we cannot further explore the relationship between serum magnesium and RA. However, a Japanese study investigated a positive linear association of dietary magnesium and serum magnesium.⁴³ In addition, prospective studies on the relationship between disease activity, severity and dietary magnesium intake in patients with RA are warranted in future. Due to these limitations, our findings need to be interpreted cautiously.

Nevertheless, our study also had advantages. First, this study was the first to investigate the non-linear, U-shaped association between dietary magnesium intake and prevalence of RA among women. In addition, we found a range of dietary magnesium intake associated with the lowest prevalence of RA in women (181–446 mg/day). Next, just as importantly, it included a large representative sample to provide sufficient statistical power to investigate the given associations and generalisability of the results. Finally, potential confounding factors were sufficiently adjusted to improve the reliability of the results.

In conclusion, based on a serial NHANES survey (1999–2016), our research identified a U-shaped relationship between dietary magnesium intake and RA in women. Dietary magnesium intake of 181–446 mg/day was associated with the lowest relative odds of RA, with increasing relative odds of RA in both directions away from this range. These results highlight the importance of moderate dietary magnesium intake in women with RA, and we expected this study to provide a new perspective for dietary policy makers to develop dietary magnesium recommendations for women at high risk of RA to delay or even prevent RA onset in the near future.

Acknowledgements The authors gratefully thank Dr Changzhong Chen, Chi Chen and Xin-Lin Chen (EmpowerStats X&Y Solutions, Boston, Massachusetts, USA) for providing statistical methodology consultation. This research was indebted to the participants of the National Health and Nutrition Examination Survey for their outstanding dedication.

Contributors GC was responsible for designing the study, guiding the manuscript development and substantially revising the paper. CH and FZ were responsible for conducting the statistical analyses, writing the first version of the manuscript and interpreting results. LL was responsible for involving in data processing and editing the manuscript. MZ contributed to data extraction and provided feedback on the study.

Funding This work was supported by the Chinese National Natural Science Foundation Project (grant number 81573850); the Science and Technology Program of Guangzhou (grant number 201904010336); the Innovative and Strong Hospital Phase II Project of the First Affiliated Hospital of Guangzhou University of Chinese Medicine, which is a part of High-level Hospital Construction Project of Guangdong Provincial Government (grant number 211010010705). These funders had no role in the design, analysis or writing of this article.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval NHANES approved by the National Center for Health Statistics Research Ethics Review Board under Continuation of Protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Open access data are available on the NHANES website.

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