


Association of serum magnesium with metabolic syndrome and the role of chronic kidney disease: A population-based cohort study with Mendelian randomization

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Abstract

Objectives: To assess the association of serum magnesium with prevalent and incident metabolic syndrome (MetS) and its individual components in the general population and to examine any effect modification by chronic kidney disease (CKD) status.

Methods: We analysed longitudinal data from the population-based KORA F4/FF4 study, including 2996 participants (387 with CKD) for cross-sectional analysis and 1446 participants (88 with CKD) for longitudinal analysis. Associations with MetS, as well as single components of MetS, were assessed by adjusted regression models. Nonlinearity was tested by restricted cubic splines and analyses were stratified by CKD. Causality was evaluated by two-sample Mendelian randomization (MR).

Results: Serum magnesium (1 SD) was inversely associated with prevalent MetS (odds ratio [OR] 0.90, 95% confidence interval [CI] 0.83, 0.98). The association was more pronounced in individuals with CKD (OR 0.75, 95% CI 0.59, 0.94). Among MetS components, serum magnesium was negatively associated with elevated fasting glucose (OR 0.78, 95% CI 0.71, 0.88) and, again, this association was more pronounced in individuals with CKD (OR 0.67, 95% CI 0.53, 0.84). Serum magnesium was not associated with incident MetS or its components. Restricted cubic spline analysis revealed a significant nonlinear inverse relationship of serum magnesium with MetS and elevated fasting glucose. MR analysis suggested an inverse causal effect of serum magnesium on MetS (OR 0.91, 95% CI 0.85, 0.97).

Conclusion: Serum magnesium is associated with prevalent, but not incident MetS, and this effect is stronger in individuals with CKD. MR analysis implies a potential, albeit weak, causal role of magnesium in MetS.

KEYWORDS

chronic kidney disease, Mendelian randomization, metabolic syndrome, population-based cohort, serum magnesium

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1 | INTRODUCTION

Increased cardiovascular risk is found in individuals with metabolic syndrome (MetS), a condition characterized by a clustering of interrelated risk factors, namely, abdominal obesity, hyperglycaemia, dyslipidaemia, and elevated blood pressure.¹ MetS affects 25% of the adult population and its prevalence continues to rise, aggravated by the obesity pandemic caused by unhealthy eating habits and a sedentary lifestyle within an obesogenic environment.^{2,3} While the exact pathogenesis of MetS is still unknown, a complex interaction of genetic, metabolic and environmental factors is suggested.⁴

The prevalence of chronic kidney disease (CKD) is dramatically increasing, affecting over 10% of the general population worldwide.⁵ Kidney impairment is considered an independent risk factor for cardiovascular disease development.⁶ Evidence demonstrated a significant association between MetS and CKD prevalence and progression, with a 5.34 odds of estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² and a 2.91 odds of albuminuria of 30 mg/g or higher.⁷ Consequently, individuals with CKD experience heightened cardiovascular morbidity and mortality, emphasizing the importance of identifying novel biomarkers to improve clinical outcomes.

Magnesium, the fourth most abundant mineral in the body, is a crucial cofactor in numerous enzymatic reactions involved in a multitude of metabolic processes. Magnesium deficiency occurs either due to inadequate intake, decreased absorption, or increased excretion.⁸ Because 80% of this mineral is lost during food processing, a significant proportion of the global population fails to meet the minimum daily magnesium requirement.⁹

Hypomagnesaemia, which usually presents as a subclinical, chronic latent deficiency, has been associated with several cardiometabolic diseases.⁸ A systematic review and meta-analysis has revealed an inverse association between magnesium and prevalent MetS.¹⁰ However, there is a scarcity of studies that specifically investigate this association in high-risk populations (e.g., men, individuals with obesity, individuals with diuretic medication intake). Furthermore, limited information is available on the association of magnesium with incident MetS and whether any putative association is causal.

The kidney is the chief organ responsible for regulating magnesium homeostasis. There is evidence that hypomagnesaemia is the predominant electrolyte abnormality observed in predialysis CKD patients, and its association with adverse clinical outcomes has been well established.^{11,12} The relationship between magnesium and MetS was previously investigated in CKD and post-kidney transplant patients.^{13,14} However, to our knowledge, no population-based study has explored this association in individuals with CKD. Given the major public health impact of both MetS and CKD, it is necessary to investigate these associations at a population-based level.

In this study, therefore, we aimed to assess the association of serum magnesium with prevalent and incident MetS and its individual components in the general population and to examine any effect modification by CKD status. We also explored the link between serum magnesium and prevalent MetS in individuals at higher risk. Moreover,

we aimed to assess the causality of this putative association using two-sample Mendelian randomization (MR) analysis.

2 | METHODS

2.1 | Study population

The Cooperative Health Research in the Region of Augsburg (baseline KORA S4, 1999–2001, first-follow-up F4, 2006–2008, second follow-up FF4, 2013–2014) is a population-based cohort study designed to assess the risk factors, prevalence and trajectories of cardiometabolic outcomes. Participants were examined at the study centre, where detailed clinical and demographic information was collected and blood was drawn.¹⁵ Since serum magnesium was not measured in the baseline S4 survey, the present analysis is based on data from KORA F4 and FF4.

KORA F4 (*n* = 3080, age 32–81 years), was used for cross-sectional analysis of prevalent MetS. KORA F4/FF4 (mean follow-up time 6.5 years) was used for longitudinal analysis of incident MetS. After applying the exclusion criteria listed in Figure S1, the respective sample sizes for cross-sectional and longitudinal analyses were *n* = 2996, of whom 387 had CKD, and *n* = 1446, of whom 88 had CKD.

The study was performed in adherence to the declaration of Helsinki, including approval from the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany) and written informed consent from all participants.

2.2 | Serum magnesium assessment

Serum magnesium was measured in mmol/L with a colorimetric assay (Chlorophosphonazo III method) with the addition of ethylene glycol tetraacetic acid (EGTA) and ethylenediaminetetraacetic acid (EDTA) as chelating agents on the Roche Cobas C system.¹⁶

2.3 | MetS assessment

According to the harmonized definition,¹⁷ MetS was defined as the presence of at least three of the following criteria: (1) waist circumference \geq 94 cm in men or \geq 80 cm in women (elevated waist circumference); (2) serum fasting triglycerides \geq 150 mg/dL (1.69 mmol/l) or the use of fibrates (elevated triglycerides); (3) serum high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dL (1.03 mmol/l) in men or $<$ 50 mg/dL (1.29 mmol/l) in women or the use of fibrates (reduced HDL-C); (4) systolic blood pressure \geq 130 mmHg or diastolic blood pressure \geq 85 mmHg or treatment with antihypertensive medication, being aware of having hypertension (elevated blood pressure); (5) fasting serum glucose level \geq 100 mg/dL (5.6 mmol/l) or intake of antidiabetic medication (elevated fasting glucose). As a sensitivity analysis, we used alternative definitions of MetS (Table S1).¹⁸

Incident MetS was determined based on the presence of at least three of the above criteria at follow-up visits after exclusion of prevalent cases at baseline. For example, incident elevated waist circumference was defined as waist circumference < 94 cm in men or < 80 cm in women at baseline and waist circumference \geq 94 cm in men or \geq 80 cm in women at the follow-up visit. Due to the exclusion of prevalent cases, the sample sizes differ between the analyses of each individual component (Table 3).

2.4 | CKD assessment

Chronic kidney disease was assessed based on the presence of either eGFR < 60 mL/min per 1.73 m² or albuminuria (urine albumin-creatinine ratio [UACR] \geq 30 mg/g), or both.¹⁹ Glomerular filtration rates were estimated from serum creatinine concentrations according to the Chronic Kidney Disease Epidemiology Collaboration equation.²⁰ As a sensitivity analysis, we used the CKD definition based on eGFR only.

2.5 | Covariates assessment

Physical activity was obtained according to the time spent per week on leisure time sport activities in summer and winter, using a four-category interview question: (1) > 2 h, (2) 1–2 h, (3) <1 h and (4) none. The total physical activity score was calculated by combining the responses for both summer and winter. Individuals with a total score of 5 or higher were categorized as 'physically inactive', otherwise 'physically active'. Smoking status was categorized as never smoker, former smoker, and current smoker. We classified alcohol consumption as none (0 g/day), moderate (0.1–39.9 g/day for men and 0.1–19.9 g/day for women), and excessive (\geq 40 g/day for men and \geq 20 g/day for women).²¹ BMI was categorized as underweight (<18.5 kg/m²), normal weight (18.5–25 kg/m²), overweight (25–30 kg/m²), and obesity (\geq 30 kg/m²). Menopausal status was classified as postmenopausal, premenopausal, and on hormone replacement therapy. Women were considered postmenopausal if they had no menses for more than 12 consecutive months, had hysterectomy with or without bilateral oophorectomy, or were over the age of 60 years.

Laboratory parameters, including total cholesterol, HDL-C, and low-density lipoprotein cholesterol (LDL-C) were measured using standardized methods as described previously.²² Serum concentrations of 25-hydroxyvitamin D (25OHD) were measured according to an electrochemiluminescence immunoassay method (Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany). We categorized serum 25OHD according to the US Endocrine Society into a deficient group (<20 ng/mL), a suboptimal group (20–29 ng/mL), and a sufficient group (>29 ng/mL).²³

2.6 | Statistical analysis

Participants' baseline characteristics are presented as mean and standard deviation (SD) or median and interquartile range (IQR) for

continuous variables, whereas categorical variables are reported as counts with corresponding percentages. Differences according to presence/incidence of MetS and CKD were evaluated by *t*-test, Mann–Whitney *U*-test or chi-squared test, where appropriate. Correlations between serum magnesium and cardiovascular risk factors were assessed by Spearman's correlation coefficients.

We used logistic regression to quantify the association between baseline serum magnesium as exposure and prevalent or incident MetS and the five underlying dichotomous components as outcomes. For the longitudinal analysis, we excluded individuals who had pre-existing MetS and its components at baseline. Furthermore, we used linear regression to quantify the association between serum magnesium and continuous variables constituting the underlying components of prevalent MetS (waist circumference, blood pressure, blood glucose, triglycerides, HDL-C) as outcomes. All analyses were conducted in the total population and according to CKD status. Confounder adjustment was as follows: Model 1 was adjusted for age and sex; Model 2 included variables in Model 1 plus smoking status, alcohol consumption, and physical activity; and Model 3 included variables in Model 2 plus diuretic medication and serum potassium. Nonlinearity was visually examined by restricted cubic splines adjusted for Model 3, with three knots (10th, 50th and 90th percentile) as quantified by a likelihood ratio test. Moreover, we performed subgroup analyses according to sex, menopausal status, CKD status, serum 25OHD status, BMI category and diuretic medication intake, and multiplicative interaction was examined.

We carried out several sensitivity analyses. In the cross-sectional analysis of serum magnesium with MetS, in addition to the full adjusted model, we performed mutual adjustment for each individual component of MetS. Furthermore, in the analyses not stratified for CKD, we adjusted for renal function-related indicators, such as serum phosphorus, serum calcium, serum sodium, serum 25OHD, eGFR and UACR. In the longitudinal analysis, we repeated the analysis between serum magnesium and incident MetS using Poisson regression given the relatively small number of MetS events.

Serum magnesium was centred and scaled per SD before regression modelling. Results are provided as odds ratios (ORs), rate ratios and β -coefficients per 1-SD increase, with corresponding 95% confidence intervals (CIs) for logistic, Poisson and linear regression, respectively. All analyses were carried out with R version 4.1.2 (R Core Team, Vienna, Austria) with a level of significance set at 5%.

2.7 | MR analysis

Mendelian randomization uses genetic variants as proxies for exposure to infer causality. Three assumptions are required: a strong association between the genetic variant and exposure; no confounding by factors affecting exposure–outcome association; and exclusive influence of the genetic variant on outcome through the exposure.²⁴

Using publicly available summary-level data from genome-wide association studies (GWAS), we conducted a two-sample MR study to assess the causal association between serum magnesium and MetS.

We identified and included six single-nucleotide polymorphisms (SNPs) that exhibited strong and independent associations with serum magnesium at genome-wide significance ($p < 5 \times 10^{-8}$). These SNPs were derived from a combined analysis of a discovery cohort ($n = 15\,366$ individuals) and a replication cohort ($n = 8463$ individuals) which could explain 1.6% of serum magnesium variance.²⁵ We then extracted the outcome summary statistics from the study on MetS by Lind et al. ($n = 291\,107$ individuals) for the selected instrumental variables.²⁶ As rs7965584 was not present in the dataset on MetS, we included a proxy rs10858938 in high linkage disequilibrium ($r^2 = 0.95$). Detailed information on the employed SNPs is given in Table S2.

As MR methods, we used inverse variance-weighted (IVW), weighted median, MR-Egger, simple mode, and weighted mode. To evaluate the robustness of our findings, we repeated the MR analysis excluding two SNPs (rs448378 and rs4072037) known to be associated with MetS components, namely, blood pressure and fasting blood sugar.²⁵ We scaled all ORs per 0.1-mmol/L increase in serum magnesium. The 'TwoSampleMR' R-package was used for analysis.²⁷

3 | RESULTS

3.1 | Characteristics of the study population

At baseline, 1052 individuals (prevalence 35%; mean age: 62.1 ± 11.4 years; 60.2% men) had prevalent MetS and during a follow-up of 6.5 years, 251 individuals (incidence rate 17%; mean age: 57.1 ± 10.8 years; 54.6% men) developed incident MetS (Table 1). Individuals with prevalent and incident MetS had a more unfavourable metabolic and cardiovascular risk profile, such as older age and higher BMI, dyslipidaemia, and vitamin D deficiency. Furthermore, participants with prevalent MetS were more likely to have CKD compared to those without MetS (22.3% vs. 7.8%; p value < 0.001). Individuals with incident MetS had a significantly lower eGFR compared to those without incident MetS (87.5 vs. 93.4; $p < 0.001$), although the prevalence of CKD was not significantly different (7.6% vs. 5.8%; $p = 0.349$). Baseline characteristics of participants with prevalent and incident MetS stratified by CKD status are shown in Tables S3 and S4, respectively.

In both the overall sample and among individuals with CKD, Spearman correlation analysis revealed a significant negative correlation between serum magnesium and fasting glucose, and positive correlations between serum magnesium and serum sodium and potassium, cholesterol, and triglyceride levels (Table S5).

3.2 | Association of serum magnesium and prevalent MetS

Logistic regression demonstrated a significant association between a 1-SD increase in serum magnesium and lower odds of prevalent MetS (OR 0.90 [95% CI 0.83, 0.98] in the fully adjusted model; Table 2). This association was more pronounced in individuals with CKD (0.75 [95% CI 0.59, 0.94]),

although a formal multiplicative interaction test was not statistically significant ($p = 0.096$). Restricted cubic spline analysis revealed that the association was nonlinear ($p = 0.028$) with protective effects reaching a plateau after a certain threshold of serum magnesium (Figure 1).

The inverse association between serum magnesium and prevalent MetS remained robust across various MetS definitions. However, in individuals with CKD, this association was attenuated and lost significance when using alternative MetS criteria (Figure S2). Mutual adjustment for individual components of MetS revealed loss of association between serum magnesium and prevalent MetS when adjusting for elevated fasting glucose (Table S6). In addition, the association between serum magnesium with MetS remained significant even after accounting for renal function-related indicators as illustrated in Table S7.

In stratified analyses, the inverse association between serum magnesium and prevalent MetS was observed in individuals at higher metabolic risk, such as men, individuals with obesity, and individuals taking diuretic medication (p value multiplicative interaction 0.424, 0.029, 0.070, respectively; Figure S3). No significant association was found according to serum 25OHD status. In women, we found no statistically significant association between serum magnesium and MetS according to menopausal status (Table S8).

3.3 | Association of serum magnesium and components of prevalent MetS

Among the MetS components, serum magnesium showed a significant inverse association with elevated fasting glucose (OR 0.78 [95% CI 0.71, 0.85]), again with a stronger effect in individuals with CKD (OR 0.67 [95% CI 0.53, 0.84]; p value interaction = 0.484). The association was nonlinear ($p = 0.013$) with a similar shaped association to that with MetS (Figure 1). There was no significant association between serum magnesium and other components of MetS (Table 2), including nonlinear associations (all $p > 0.1$; Figure 1).

For continuous variables constituting the underlying dichotomous components of MetS, there was a significant association between increased serum magnesium and lower fasting glucose levels (β -3.10 mg/dL per 1-SD in serum magnesium [95% CI -3.72, -2.48]) in the overall sample, again with a stronger effect in individuals with CKD (β -6.11 [95% CI -9.08, -3.13]; Table S9). Moreover, in the overall sample and in individuals without CKD, serum magnesium was also associated with lower waist circumference (Table S9).

When CKD was defined based on eGFR only, the observed association of serum magnesium with MetS and elevated fasting glucose among individuals with CKD was attenuated to the point of becoming nonsignificant (Table S10).

3.4 | Association of serum magnesium and incident MetS

In our analysis of incident MetS and its components, we had varying sample sizes due to the exclusion of prevalent cases at baseline: MetS

TABLE 1 Descriptive statistics of the study participants by metabolic syndrome prevalence and incidence.

	Cross-sectional analysis (N = 2996)			Longitudinal analysis (N = 1446)		
	Prevalent MetS	No MetS	p value	Incident MetS	No MetS	p value
	(N = 1052)	(N = 1944)		(N = 251)	(N = 1195)	
Demographics						
Age, years	62.1 (11.4)	53.0 (13.0)	<0.001	57.1 (10.8)	50.5 (11.9)	<0.001
Male, n (%)	633 (60.2)	814 (41.9)	<0.001	137 (54.6)	476 (39.8)	<0.001
Components of MetS, n (%)						
Elevated waist circumference	1009 (95.9)	1036 (53.3)	<0.001	68 (27.1)	202 (16.9)	<0.001
Elevated blood pressure	897 (85.3)	566 (29.1)	<0.001	91 (36.3)	93 (7.8)	<0.001
Elevated fasting glucose	783 (74.4)	204 (10.5)	<0.001	165 (65.7)	156 (13.1)	<0.001
Elevated triglycerides	611 (58.1)	140 (7.2)	<0.001	87 (34.7)	51 (4.3)	<0.001
Reduced HDL-C	431 (41.0)	172 (8.8)	<0.001	19 (7.6)	9 (0.8)	<0.001
Anthropometrics						
Waist circumference, cm	103.7 (11.9)	88.5 (12.0)	<0.001	95.7 (10.7)	86.5 (11.4)	<0.001
Waist-to-hip ratio	0.94 (0.07)	0.85 (0.08)	<0.001	0.90 (0.07)	0.84 (0.08)	<0.001
BMI, kg/m ²	30.6 (4.6)	26.0 (4.1)	<0.001	28.4 (4.2)	25.4 (3.8)	<0.001
BMI category ^a , n (%)			<0.001			<0.001
Normal weight	70 (6.7)	863 (44.6)		50 (19.9)	602 (50.8)	
Overweight	472 (44.9)	783 (40.3)		131 (52.2)	456 (38.2)	
Obesity	510 (48.5)	288 (14.8)		70 (27.9)	128 (10.7)	
Lipid profile						
Total cholesterol, mmol/L	5.67 (1.07)	5.54 (0.99)	0.001	5.75 (1.04)	5.46 (0.93)	<0.001
LDL-C, mmol/L	3.63 (0.92)	3.46 (0.88)	<0.001	3.73 (0.91)	3.39 (0.84)	<0.001
HDL-C, mmol/L	1.24 (0.31)	1.56 (0.36)	<0.001	1.44 (0.32)	1.58 (0.36)	<0.001
Triglycerides, mmol/L	2.00 (1.17)	1.07 (0.58)	<0.001	1.28 (0.62)	1.00 (0.48)	<0.001
Kidney function						
eGFR, mL/min/1.73 m ²	81.0 (17.0)	91.5 (15.4)	<0.001	87.5 (14.9)	93.4 (14.1)	<0.001
UACR, median (IQR) mg/g	7.7 (4.3, 16.7)	5.3 (3.4, 9.4)	<0.001	4.9 (3.2, 8.8)	5.0 (3.4, 8.5)	0.670
CKD, n (%)	235 (22.3)	152 (7.8)	<0.001	19 (7.6)	69 (5.8)	0.349
Diuretic medication, n (%)	358 (34.0)	172 (8.8)	<0.001	42 (16.7)	58 (4.9)	<0.001
Behavioural risk factors						
Smoking, n (%)			<0.001			0.087
Never	431 (41.0)	820 (42.2)		93 (37.1)	528 (44.2)	
Former	481 (45.7)	736 (37.9)		103 (41.0)	455 (38.1)	
Current	140 (13.3)	388 (20.0)		55 (21.9)	212 (17.7)	
Alcohol consumption, n (%)			0.003			0.745
None	352 (33.5)	546 (28.1)		71 (28.3)	320 (26.8)	
Moderate	509 (48.4)	1062 (54.6)		136 (54.2)	679 (56.8)	
Excessive	191 (18.2)	336 (17.3)		44 (17.5)	196 (16.4)	
Physically active	498 (47.3)	1143 (58.8)	<0.001	145 (57.8)	745 (62.3)	0.200
Blood markers						
HbA1c, %	5.9 (0.8)	5.4 (0.4)	<0.001	5.5 (0.3)	5.3 (0.3)	<0.001
Serum magnesium, mmol/L	0.906 (0.071)	0.911 (0.059)	0.014	0.917 (0.057)	0.911 (0.057)	0.137
Serum sodium, mmol/L	139.0 (2.6)	139.1 (2.5)	0.172	138.9 (2.6)	139.2 (2.4)	0.151
Serum potassium, mmol/L	4.19 (0.31)	4.18 (0.26)	0.124	4.16 (0.26)	4.17 (0.25)	0.545
Serum phosphorus, mmol/L	1.07 (0.17)	1.10 (0.16)	<0.001	1.09 (0.16)	1.10 (0.15)	0.209
Serum calcium, mmol/L	2.41 (0.12)	2.39 (0.11)	<0.001	2.39 (0.11)	2.39 (0.11)	0.575

TABLE 1 (Continued)

	Cross-sectional analysis (N = 2996)			Longitudinal analysis (N = 1446)		
	Prevalent MetS	No MetS	p value	Incident MetS	No MetS	p value
	(N = 1052)	(N = 1944)		(N = 251)	(N = 1195)	
Serum 25OHD, ng/mL	17.4 (8.4)	20.3 (9.8)	<0.001	19.6 (8.1)	20.7 (9.8)	0.079
Vitamin D category, n (%)			<0.001			0.028
Sufficient	97 (9.2)	327 (16.8)		30 (12.0)	214 (17.9)	
Suboptimal	250 (23.8)	575 (29.6)		73 (29.1)	372 (31.1)	
Deficient	705 (67.0)	1042 (53.6)		148 (59.0)	609 (51.0)	

Note: Values are reported as mean (SD), unless otherwise indicated. Number of missing values for UACR was 14 and five for cross-sectional and longitudinal datasets, respectively. Elevated waist circumference: waist circumference \geq 94 cm in men or \geq 80 cm in women. Elevated blood pressure: systolic blood pressure \geq 130 mmHg or diastolic blood pressure \geq 85 mmHg or treatment with antihypertensive medication being aware of having hypertension. Elevated fasting glucose: fasting serum glucose level \geq 100 mg/dL (5.6 mmol/l) or intake of antidiabetic medication. Elevated triglycerides: serum fasting triglycerides \geq 150 mg/dL (1.69 mmol/l) or the use of fibrates. Reduced HDL-C: serum HDL-C $<$ 40 mg/dL (1.03 mmol/l) in men or $<$ 50 mg/dL (1.29 mmol/l) in women or the use of fibrates. Excessive alcohol consumption: Men with an alcohol intake \geq 30 g/day and women \geq 20 g/day. Vitamin D deficiency: serum 25OHD $<$ 20 ng/mL.

Abbreviations: 25OHD, 25-hydroxyvitamin D; BMI, body mass index; CKD, chronic kidney disease; eGFR, glomerular filtration rate estimated by creatinine; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; UACR, urine albumin-creatinine ratio.

^aNumber of individuals classified as underweight was 10 in the cross-sectional dataset and nine in the longitudinal dataset.

($n = 1446$), elevated waist circumference ($n = 736$), elevated blood pressure ($n = 1186$), elevated fasting glucose ($n = 1463$), elevated triglycerides ($n = 1617$), and reduced HDL-C ($n = 1707$). There was no significant association between serum magnesium and incident MetS or its components (Tables 3 and S11).

3.5 | Mendelian randomization

Genetically predicted serum magnesium was causally associated with lower odds of MetS in both IVW (OR per 0.1-mmol/L increase: 0.91 [95% CI 0.85, 0.97]) and weighted median MR analyses (0.91 [0.84, 0.99]; Table 4). MR-Egger analysis showed no evidence of directional pleiotropy (MR-Egger intercept: 0.006; $p = 0.610$). Exclusion of SNPs rs448378 and rs4072037 that were associated with components of MetS did not change the results in either the IVW or the weighted median analysis (Table 4).

In a single SNP analysis, only rs13146355 reached statistical significance (OR: 0.87 [95% CI 0.77, 0.99]; Figure S4). No significant heterogeneity was observed between the estimates from the individual SNPs (p heterogeneity = 0.975).

4 | DISCUSSION

In this comprehensive analysis of data from a population-based study, we have shown that serum magnesium was associated with prevalent MetS. The effect was more prominent in individuals with CKD and in those at higher metabolic risk. Although MR analyses indicated causality, we failed to find an association with incident MetS.

In line with our findings, a recent cross-sectional study including 1000 adults, found that a 1-SD increment of serum magnesium was

associated with reduced odds of MetS (OR: 0.70 [95% CI 0.57–0.85]).²⁸ Additionally, a meta-analysis including 3487 individuals found that serum magnesium was approximately 0.19 mg/dL lower in participants with MetS compared to those without MetS, although significant heterogeneity between studies was observed.¹⁰ Notably, there is currently no evidence for the relationship between serum magnesium and incident MetS. Nevertheless, findings from longitudinal studies on dietary magnesium intake indicated a significant inverse relationship with incident MetS.^{29,30} Our MR analysis also provided further evidence for this association, revealing a negative causal link between serum magnesium and MetS. While the exact mechanisms remain inconclusive, the beneficial effect of magnesium on MetS potentially acts through the MetS components. A randomized clinical trial demonstrated that oral magnesium supplementation improved MetS by reducing blood pressure, hyperglycaemia, and hypertriglyceridaemia.³¹ In the present study, however, we only found a significant protective effect of serum magnesium on elevated fasting glucose, as reported previously.³² This observation was further supported by the results of the mutual adjustment, revealing the loss of significance in the association between serum magnesium and prevalent MetS after adjusting for elevated fasting glucose. This underscores the role of elevated fasting glucose as the main driver of this association. Magnesium plays a vital role in insulin action and pancreatic β -cell function, acting as a critical cofactor for numerous enzymes involved in carbohydrate metabolism.³³ Magnesium deficiency has been observed to decrease glucose utilization in skeletal muscles and fat tissue, resulting in insulin resistance.³³ Furthermore, magnesium deficiency was shown to increase inflammation and oxidative stress, common pathways leading to insulin resistance.³⁴ Indeed, a population-based prospective study indicated that reduced serum magnesium levels were linked to an increased risk of prediabetes and diabetes, with insulin resistance acting as a mediating factor.³⁵

TABLE 2 Results of the multivariable logistic regression for the association between serum magnesium and prevalent metabolic syndrome and its components in the total population and stratified by chronic kidney disease status.

	Cross-sectional analysis (N = 2996)		CKD (N = 387)		No CKD (N = 2609)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Metabolic syndrome	n = 1052		n = 235		n = 817	
Model 1	0.88 (0.81, 0.95)	0.002	0.72 (0.57, 0.90)	0.001	0.93 (0.85, 1.01)	0.092
Model 2	0.89 (0.82, 0.96)	0.003	0.74 (0.58, 0.92)	0.008	0.93 (0.85, 1.01)	0.097
Model 3	0.90 (0.83, 0.98)	0.019	0.75 (0.59, 0.94)	0.014	0.94 (0.86, 1.03)	0.200
Elevated waist circumference	n = 2045		n = 312		n = 1733	
Model 1	0.95 (0.87, 1.03)	0.195	0.96 (0.73, 1.25)	0.742	0.94 (0.86, 1.05)	0.188
Model 2	0.95 (0.87, 1.03)	0.223	0.99 (0.75, 1.31)	0.958	0.94 (0.86, 1.03)	0.181
Model 3	0.95 (0.87, 1.04)	0.239	1.01 (0.74, 1.36)	0.978	0.94 (0.86, 1.03)	0.161
Elevated blood pressure	n = 1463		n = 311		n = 1440	
Model 1	0.95 (0.88, 1.03)	0.254	0.88 (0.68, 1.14)	0.335	0.97 (0.89, 1.06)	0.507
Model 2	0.96 (0.88, 1.04)	0.276	0.93 (0.70, 1.21)	0.571	0.97 (0.89, 1.06)	0.485
Model 3	1.00 (0.91, 1.10)	0.977	0.98 (0.72, 1.32)	0.907	1.00 (0.91, 1.10)	0.981
Elevated fasting glucose	n = 987		n = 214		n = 773	
Model 1	0.77 (0.71, 0.84)	<0.001	0.66 (0.53, 0.83)	0.001	0.80 (0.73, 0.87)	<0.001
Model 2	0.77 (0.71, 0.84)	<0.001	0.66 (0.52, 0.83)	0.001	0.79 (0.72, 0.87)	<0.001
Model 3	0.78 (0.71, 0.85)	<0.001	0.67 (0.53, 0.84)	0.001	0.80 (0.73, 0.88)	<0.001
Elevated triglycerides	n = 751		n = 143		n = 608	
Model 1	1.01 (0.93, 1.10)	0.760	0.96 (0.78, 1.18)	0.707	1.03 (0.94, 1.14)	0.472
Model 2	1.02 (0.94, 1.11)	0.654	0.97 (0.79, 1.20)	0.786	1.04 (0.94, 1.14)	0.456
Model 3	1.03 (0.94, 1.12)	0.549	0.96 (0.78, 1.19)	0.726	1.04 (0.95, 1.15)	0.381
Reduced HDL-C	n = 603		n = 115		n = 488	
Model 1	0.93 (0.85, 1.02)	0.130	1.05 (0.84, 1.31)	0.686	0.92 (0.83, 1.01)	0.082
Model 2	0.95 (0.87, 1.04)	0.245	1.09 (0.87, 1.37)	0.471	0.92 (0.83, 1.03)	0.121
Model 3	0.96 (0.88, 1.06)	0.424	1.12 (0.89, 1.41)	0.334	0.93 (0.84, 1.03)	0.168

Note: Model 1 was adjusted for age and sex. Model 2: Model 1 + smoking status, physical activity, and alcohol consumption. Model 3: Model 2 + Serum potassium and diuretic medication. Serum magnesium was standardized. The coefficients represent the OR of prevalent metabolic syndrome and its components according to a 1-SD increase of serum magnesium. CKD was defined based on estimated glomerular filtration rate and urine albumin-creatinine ratio. Elevated waist circumference: waist circumference ≥ 94 cm in men or ≥ 80 cm in women. Elevated blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment with antihypertensive medication being aware of having hypertension. Elevated fasting glucose: fasting serum glucose level ≥ 100 mg/dL (5.6 mmol/l) or intake of antidiabetic medication. Elevated triglycerides: serum fasting triglycerides ≥ 150 mg/dL (1.69 mmol/l) or the use of fibrates. Reduced HDL-C: serum HDL-C < 40 mg/dL (1.03 mmol/l) in men or < 50 mg/dL (1.29 mmol/l) in women or the use of fibrates.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.

Our results suggested an inverse association of serum magnesium with waist circumference when modelled as a continuous variable. Moreover, in stratified analysis, serum magnesium showed a protective effect against MetS in individuals with obesity, as measured by BMI. Randomized clinical trials report inconsistent results on the effects of magnesium supplementation on MetS in individuals with obesity. Some studies indicated that magnesium supplementation improves cardiometabolic risk markers in individuals with overweight or obesity, whereas another study did not support this conclusion.^{13,36,37} Interestingly, magnesium supplementation in individuals with overweight was shown to elicit changes in gene expression and proteomic profiling, consistent with favourable effects on various metabolic pathways.³⁸

We did not find an association between serum magnesium and elevated lipid profile. Currently, there is no consensus on the effect of magnesium on lipid profile, as reported by a recent extensive systematic review.³⁹ Despite existing evidence, we failed to find an association between serum magnesium and elevated blood pressure. A systematic review and meta-analysis, including studies on dietary magnesium intake, serum magnesium, or both, revealed an inverse dose-response relationship between dietary magnesium intake and incident hypertension. However, the association was marginal for serum magnesium.⁴⁰

Our study showed an inverse association of serum magnesium with MetS and elevated fasting glucose in individuals with CKD.

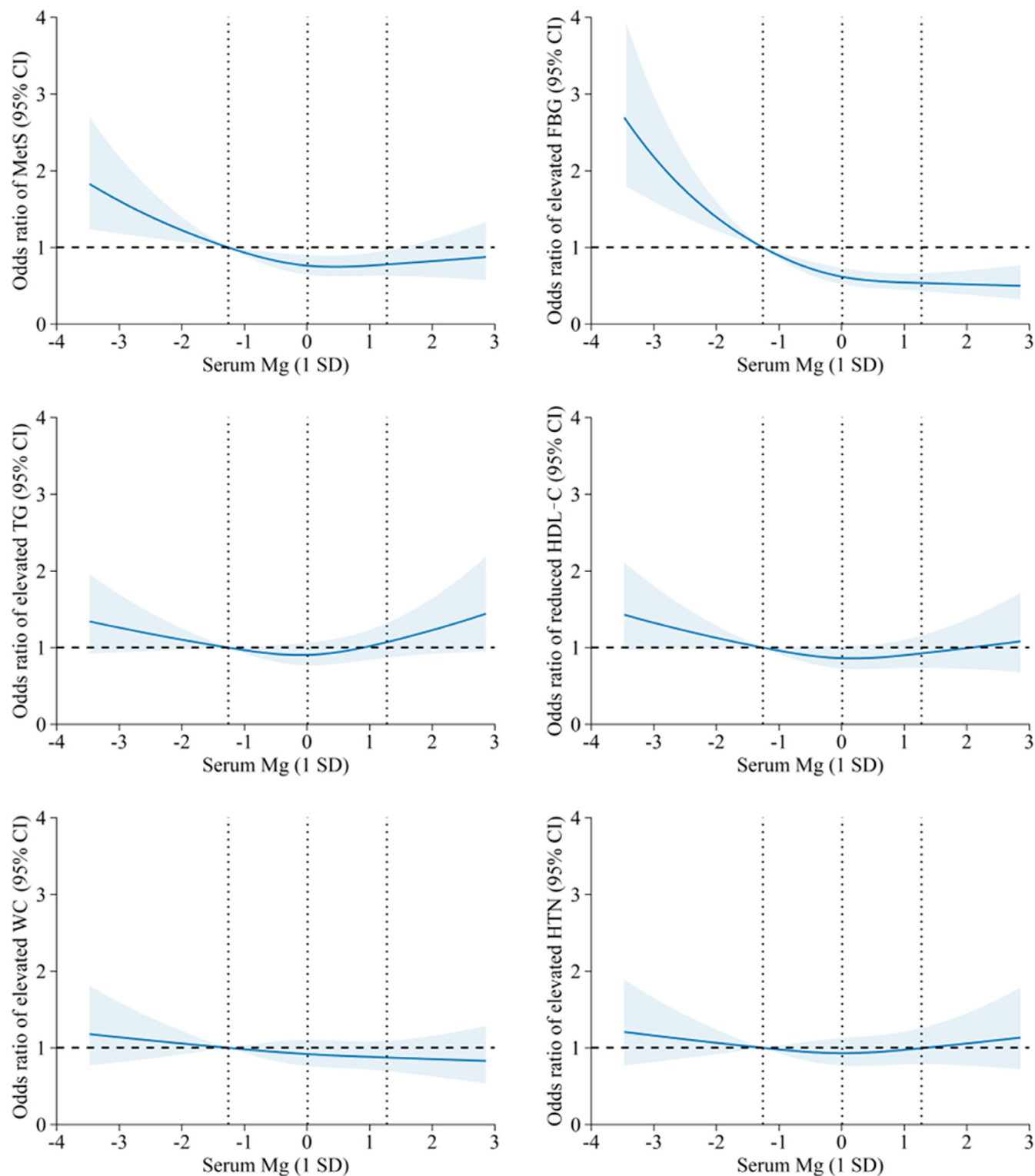


FIGURE 1 Restricted cubic spline showing the exposure–response functions between serum magnesium (1 SD) and prevalent metabolic syndrome (MetS) and its components using logistic regression models adjusted for age, sex, smoking status, physical activity, alcohol consumption, serum potassium and diuretic medication (corresponding to Model 3). Three knots were applied at the 10th, 50th and 90th percentiles corresponding to -1.26 , 0.01 and 1.28 of standardized serum magnesium (reference is the 10th percentile). Solid lines indicate odds ratios, and shaded areas indicate 95% confidence intervals (CIs). Elevated waist circumference (WC): WC ≥ 94 cm in men or ≥ 80 cm in women. Elevated blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment with antihypertensive medication being aware of having hypertension. Elevated fasting glucose: fasting serum glucose level ≥ 100 mg/dL (5.6 mmol/l) or intake of antidiabetic medication. Elevated triglycerides (TG): serum fasting TG ≥ 150 mg/dL (1.69 mmol/l) or the use of fibrates. Reduced high-density lipoprotein cholesterol (HDL-C): serum HDL-C < 40 mg/dL (1.03 mmol/l) in men or < 50 mg/dL (1.29 mmol/l) in women, or the use of fibrates. FBG, fasting blood glucose; Mg, magnesium; HTN, hypertension.

TABLE 3 Results of the multivariable logistic regression for the association between serum magnesium and incident metabolic syndrome and its components in the total population and stratified by chronic kidney disease status.

	OR (95% CI)		OR (95% CI)		OR (95% CI)	
	All (n = 1446)	p value	CKD (n = 88)	p value	No CKD (n = 1358)	p value
Incident MetS	n = 251		n = 19		n = 232	
Model 1	1.03 (0.90, 1.19)	0.673	0.73 (0.43, 1.25)	0.262	1.06 (0.92, 1.23)	0.414
Model 2	1.02 (0.89, 1.17)	0.770	0.64 (0.33, 1.19)	0.168	1.05 (0.91, 1.21)	0.527
Model 3	1.02 (0.89, 1.18)	0.778	0.65 (0.33, 1.22)	0.188	1.05 (0.90, 1.21)	0.529
Incident elevated waist circumference	All (n = 736)		CKD (n = 46)		Non-CKD (n = 690)	
	n = 285		n = 19		n = 266	
Model 1	1.09 (0.94, 1.27)	0.248	1.44 (0.76, 3.00)	0.285	1.07 (0.91, 1.25)	0.405
Model 2	1.09 (0.94, 1.27)	0.269	2.28 (0.81, 8.61)	0.162	1.07 (0.91, 1.25)	0.406
Model 3	1.08 (0.93, 1.26)	0.308	n.p.	n.p.	1.06 (0.91, 1.25)	0.431
Incident elevated blood pressure	All (n = 1186)		CKD (n = 60)		Non-CKD (n = 1126)	
	n = 228		n = 20		n = 208	
Model 1	0.98 (0.84, 1.14)	0.772	0.72 (0.37, 1.31)	0.305	0.99 (0.85, 1.16)	0.898
Model 2	0.97 (0.84, 1.13)	0.739	0.64 (0.31, 1.21)	0.192	0.98 (0.84, 1.15)	0.833
Model 3	0.97 (0.84, 1.13)	0.708	0.70 (0.34, 1.38)	0.317	0.99 (0.84, 1.15)	0.853
Incident elevated fasting glucose	All (n = 1463)		CKD (n = 101)		Non-CKD (n = 1362)	
	n = 401		n = 31		n = 370	
Model 1	0.92 (0.82, 1.04)	0.182	0.84 (0.53, 1.31)	0.446	0.92 (0.82, 1.05)	0.250
Model 2	0.91 (0.81, 1.03)	0.133	0.80 (0.48, 1.30)	0.375	0.92 (0.81, 1.04)	0.180
Model 3	0.91 (0.81, 1.03)	0.130	0.80 (0.47, 1.31)	0.373	0.92 (0.81, 1.04)	0.188
Incident elevated triglycerides	All (n = 1617)		CKD (n = 126)		Non-CKD (n = 1491)	
	n = 185		n = 16		n = 169	
Model 1	1.00 (0.86, 1.17)	0.989	1.09 (0.59, 1.70)	0.994	1.00 (0.85, 1.17)	0.975
Model 2	0.99 (0.85, 1.16)	0.917	0.99 (0.56, 1.71)	0.957	0.99 (0.84, 1.16)	0.874
Model 3	1.00 (0.85, 1.16)	0.961	1.00 (0.57, 1.74)	0.999	0.99 (0.84, 1.17)	0.929
Incident reduced HDL-C	All (n = 1707)		CKD (n = 136)		Non-CKD (n = 1571)	
	n = 45		n < 5^a		n = 41	
Model 1	1.13 (0.84, 1.53)	0.425			1.19 (0.87, 1.62)	0.282
Model 2	1.12 (0.83, 1.51)	0.468			1.18 (0.86, 1.60)	0.304
Model 3	1.09 (0.80, 1.46)	0.594			1.14 (0.84, 1.56)	0.395

Note: Model 1 was adjusted for age and sex. Model 2: Model1 + Smoking status, physical activity, and alcohol consumption. Model 3: Model 2 + Serum potassium and diuretic medications. Serum magnesium was standardized. The coefficients represent the OR of incident metabolic syndrome and its components according to a 1 SD increase of serum magnesium. CKD was defined based on baseline estimated glomerular filtration rate and urine albumin-creatinine ratio. Incident MetS and its components were modelled after exclusion of prevalent cases at baseline. Incident elevated waist circumference: Waist circumference < 94 cm in men or < 80 cm in women at baseline and waist circumference ≥ 94 cm in men or ≥ 80 cm in women at the follow-up visit. Incident elevated blood pressure: Systolic blood pressure < 130 mmHg or diastolic blood pressure < 85 mmHg or no hypertension medication at baseline and systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment with antihypertensive medication being aware of having hypertension at follow up visit. Incident elevated fasting glucose: Fasting serum glucose level < 100 mg/dL or no diabetic medication at baseline and fasting serum glucose level ≥ 100 mg/dL or intake of antidiabetic medication at follow up visit. Incident elevated triglycerides: Serum fasting triglycerides < 150 mg/dL or no fibrates medication at baseline and Serum fasting triglycerides ≥ 150 mg/dL or the use of fibrates at follow up visit. Incident reduced HDL-C: Serum HDL-C ≥ 40 mg/dL in men or ≥ 50 mg/dL in women or no fibrates intake at baseline and serum HDL-C < 40 mg/dL in men or < 50 mg/dL in women or the use of fibrates at follow up visit. n.p. modelling not possible.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, odds ratio.

^aNo modelling was possible due to low sample size.

TABLE 4 Mendelian randomization results showing associations between genetically determined levels of serum magnesium and metabolic syndrome.

Method	Six SNPs			Four SNPs ^a		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Inverse variance-weighted	0.91	(0.85, 0.97)	0.004	0.90	(0.84, 0.98)	0.011
MR Egger	0.85	(0.67, 1.07)	0.253	0.84	(0.48, 1.47)	0.608
Weighted median	0.91	(0.84, 0.99)	0.020	0.90	(0.82, 0.99)	0.045
Simple mode	0.92	(0.82, 1.02)	0.179	0.93	(0.81, 1.05)	0.290
Weighted mode	0.91	(0.83, 1.00)	0.083	0.91	(0.82, 1.02)	0.204

Abbreviations: CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SNP, single nucleotide polymorphism.

^ars448378 (associated with systolic blood pressure) and rs4072037 (associated with diastolic blood pressure and fasting glucose) were excluded from analysis. ORs and 95% CIs were scaled per 0.1-mmol/L increase in serum magnesium.

Analogously, studies have demonstrated an inverse association of serum magnesium with various surrogate parameters of cardiovascular disease in CKD patients.⁴¹ However, a randomized clinical trial revealed that 3 months of magnesium supplementation did not improve MetS in patients with CKD that had prediabetes and obesity.¹³ Similarly, another study in kidney transplant patients indicated that dietary magnesium intake did not exhibit a significant relationship with the risk of MetS over 1 year of follow-up.¹⁴ These findings may be attributed to the relatively short follow-up duration and the specific selection of participants. Generally, it is important to note that findings relating to dietary magnesium intake are not directly translatable to findings from serum magnesium levels, since these two parameters do not correlate well.⁴²

Disturbance in magnesium balance is common in individuals with CKD, primarily due to impaired renal reabsorption, diuretic use, and changes in diet.⁴³ In fact, Oka et al. reported that hypomagnesaemia was the most frequent electrolyte abnormality among 2126 predialysis patients, and positive proteinuria was identified as an independent risk factor for magnesium wasting. Interestingly, this association was mediated by urinary tubular markers representing tubular dysfunction.¹¹ This could potentially explain the attenuation and loss of association of serum magnesium with MetS and elevated fasting glucose in our study when CKD was defined based on eGFR alone, without considering proteinuria. It is, therefore, reasonable to consider that magnesium may have a protective effect in individuals susceptible to hypomagnesaemia. Nevertheless, we cannot rule out the hypothesis that hypomagnesaemia could be a consequence of MetS, exacerbated by the presence of other comorbidities, as we were unable to establish a prospective association. Moreover, it should be noted that our definition of CKD was based on biomarkers of renal function only, whereas generally CKD also comprises heterogeneous phenotypes such as nephrotic syndrome or chronic nephritis. Unfortunately, information on these phenotypes was not available in our study.

Vitamin D biosynthesis, activation and transport are dependent on magnesium bioavailability. Similarly, vitamin D is necessary for the intestinal uptake and absorption of magnesium.⁴⁴ Dysregulation in any of these nutrients has been connected to MetS,¹⁰ yet research exploring their combined interaction effect on MetS remains limited. Among 126 patients with diabetes, a significant increase in serum

magnesium was observed after consumption of vitamin D supplements for 6 months.⁴⁵ Among women with obesity, low serum magnesium was significantly modified by vitamin D injection.⁴⁶ Our results, however, indicated no effect modification of serum magnesium on MetS by vitamin D status.

We found the inverse association of serum magnesium with MetS and elevated fasting glucose to be nonlinear, indicating that potential protective effects of high magnesium levels remain stable after a certain threshold. In line with this, a prospective cohort study in 5044 participants demonstrated a nonlinear relationship of serum magnesium with diabetes and insulin resistance.⁴⁷ On the other hand, Negrea et al. found that serum magnesium <1.9 mg/dL and >2.1 mg/dL was associated with all-cause mortality in a large cohort of patients with CKD.⁴⁸

The observed lack of longitudinal association between serum magnesium and MetS in our study was unexpected, given a—albeit weak—causal relation. However, it could be attributed to several factors, including insufficient statistical power, heterogeneity of the sample, variations in the duration of the disease, and changes in risk factor distribution over time. Notably, within the 6.5-year follow-up period, the determination of the precise timing of MetS development was impossible, posing a challenge to capture the latency period. The dynamic nature of risk factor distribution over time, particularly changes in magnesium levels, further complicated the matter.

While we observed a more pronounced association between serum magnesium and MetS among participants with CKD, a formal test for multiplicative interaction did not reach statistical significance, probably owing to the relatively small sample size of the CKD group. Additionally, this association dissipated when employing alternative MetS definitions. Consequently, further research is warranted to thoroughly explore the potential effect modification by CKD status.

We performed MR using publicly available association data from GWAS for MetS and magnesium. However, it is important to note that the various components of MetS exhibit both common and distinct genetic associations.^{49,50} Conducting MR on the individual components and utilizing genetic instruments specific to each underlying trait will offer additional insights into the relationship between serum magnesium and MetS.

In conclusion, we found that higher serum magnesium levels were associated with a lower risk of MetS, particularly in individuals with CKD. MR analysis showed that this association is potentially causal; however, we failed to find associations with incident MetS. Serum magnesium thus has the potential to serve as a diagnostic marker for metabolic impairment. Larger, well-characterized longitudinal cohorts are warranted to further establish its role as a prognostic marker.

AUTHOR CONTRIBUTIONS

Conceptualization: Nuha Shugaa Addin and Susanne Rospleszcz; Methodology: Nuha Shugaa Addin, Fiona Niedermayer and Susanne Rospleszcz; Formal analysis: Nuha Shugaa Addin; Resources: Barbara Thorand, Jakob Linseisen, Jochen Seissler and Annette Peters; Writing—original draft preparation: Nuha Shugaa Addin and Susanne Rospleszcz; Writing—review and editing: Nuha Shugaa Addin, Fiona Niedermayer, Barbara Thorand, Jakob Linseisen, Jochen Seissler, Annette Peters and Susanne Rospleszcz; Supervision: Jochen Seissler, Annette Peters and Susanne Rospleszcz; Funding acquisition: Barbara Thorand, Jakob Linseisen, Jochen Seissler and Annette Peters. All authors have read and agreed on the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15497>.

DATA AVAILABILITY STATEMENT

The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request from the KORA database by means of a project agreement. Requests should be sent to kora.passt@helmholtz-muenchen.de and are subject to approval by the KORA Board. The GWAS summary data for serum magnesium are available from the GWAS Catalog, study accession GCST000756 (<https://www.ebi.ac.uk/gwas/studies/>

GCST000756). Genome-Wide Association Study of MetS was extracted from the UK Biobank, study accession GCST009602 (<https://www.ebi.ac.uk/gwas/studies/GCST009602>).

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SUPPORTING INFORMATION

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