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MR-PheWAS for the causal effects of serum magnesium on multiple disease outcomes in Caucasian descent

MR-PheWAS (UK Biobank cohort)

The PPI network (Serum Mg and cataracts)

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Highlights

MR-PheWAS implicates a causal role of serum Mg in 11 disease groups/outcomes

Our study indicates gender-specific effects of 9 disease groups/outcomes

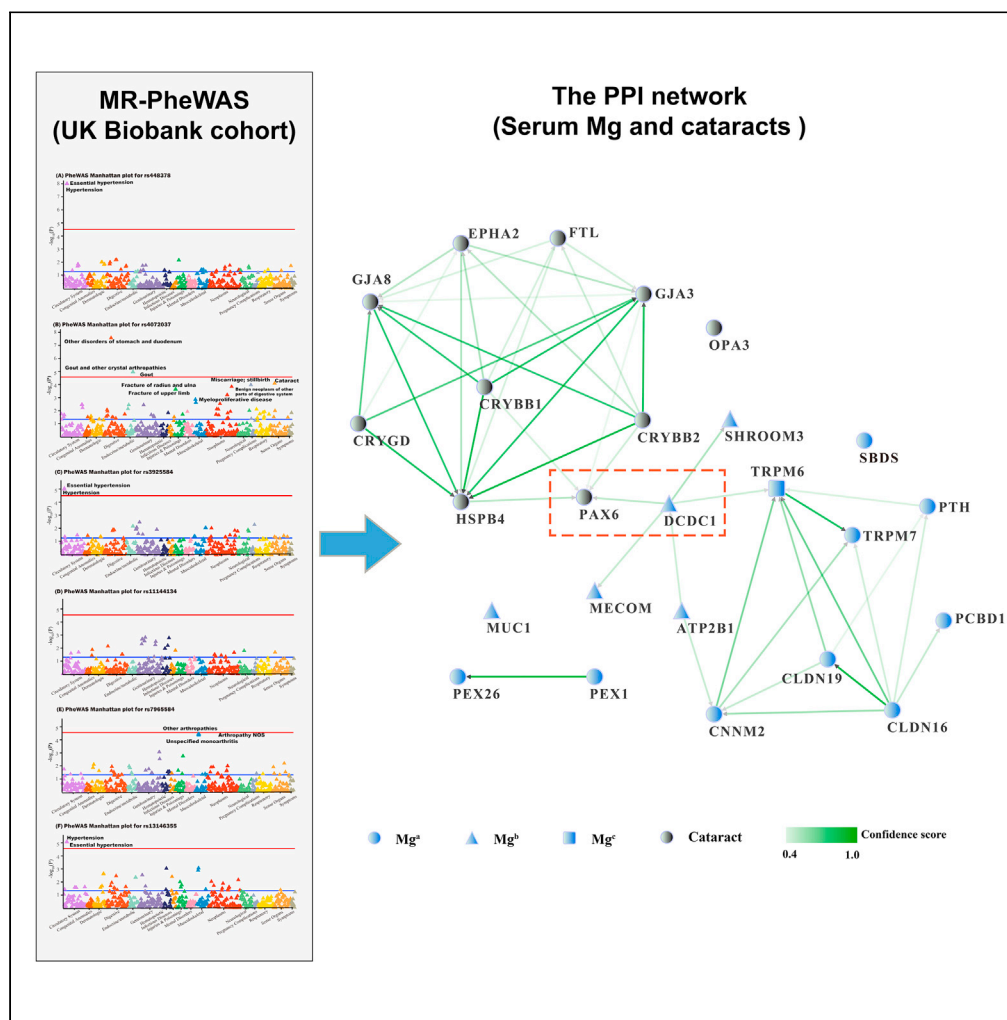Mg intervention may promote cataracts treatments through the *DCDC1* and *PAX6* genes

Article

MR-PheWAS for the causal effects of serum magnesium on multiple disease outcomes in Caucasian descent

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SUMMARY

Magnesium is integral to many physiological processes, whereas variations in its levels, even within the normal range, can have critical implications for health. To explore the broad clinical effects of varying serum magnesium levels, we performed a two-sample Mendelian randomization and phenome-wide association study (MR-PheWAS) in the UK Biobank cohort. In total, MR-PheWAS analysis implicated a causal role of serum magnesium levels in five disease groups and six disease outcomes. In addition, our study indicated the gender-specific effects of nine disease groups/outcomes in MR estimated effects. The protein-protein interaction network demonstrated an interaction between the serum magnesium-associated gene *DCDC1* and the cataract- associated gene *PAX6*. The present study verified several previously reported disease outcomes and identified novel potential disease outcomes for serum magnesium levels. The *DCDC1* gene and the *PAX6* gene may be the new targets for promoting the treatments of cataracts using magnesium intervention.

INTRODUCTION

As an essential mineral in humans, magnesium is the fourth most abundant mineral and the second most abundant intracellular divalent cation (Volpe, 2013). Magnesium is consumed primarily through food, especially those rich in dietary fiber, unrefined (whole) grains, nonstarchy vegetables (spinach), fruits, nuts, legumes, potatoes (tubers), and dairy products (Wark et al., 2012). The recommended dietary allowance of magnesium is 80 mg/d for children aged 1–3 y, 130 mg/d for children aged 4–8 y, 240 mg/d for juniors aged 9–13 y, and 420 mg/d (males) or 320 mg/d (females) for adults aged 31 y and older (Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference I, 1997). Generally, magnesium is mostly stored in the bone, tissues, organs, and blood, while mainly being excreted through the urine (Volpe, 2013). Moreover, magnesium is mainly involved in the processes of protein synthesis, cellular energy production and storage, reproduction, DNA and RNA synthesis, and stabilizing mitochondrial membranes (Bohl and Volpe, 2002; Burgess et al., 2015; Chubanov et al., 2005; Newhouse and Finstad, 2000). In addition, magnesium plays a critical role in maintaining normal nerve and muscle function, cardiac excitability (normal heart rhythm), neuromuscular conduction, muscular contraction, vasomotor tone, blood pressure, bone integrity, and glucose and insulin metabolism (Barbagallo et al., 2003; Bohl and Volpe, 2002; Burgess et al., 2015; Chubanov et al., 2005; Guerrero-Romero and Rodriguez-Moran, 2000, 2002; He et al., 2006; Lopez-Ridaura et al., 2004; McCarty, 2005; Murakami et al., 2005; Newhouse and Finstad, 2000; Paolisso and Barbagallo, 1997; Soltani et al., 2005).

In this regard, magnesium deficiencies and excesses have been associated with some chronic diseases. A comprehensive search strategy study and a randomized, placebo-controlled clinical trial have both demonstrated that magnesium supplementation has significant effects on relieving migraine headaches (Pringsheim et al., 2012; Tarighat Esfanjani et al., 2012). A Mendelian randomization (MR) study in European ancestry individuals supported the longstanding hypothesis that magnesium supplementation can increase the risk of developing both rheumatoid arthritis and Alzheimer's disease, using databases of the International Cohorts for Heart and Aging Research in Genomic Epidemiology Alliance and the International Genomics of Alzheimer's Project, respectively (Cheng et al., 2019). Based on the Kuopio Ischaemic Heart Disease cohort recruited in eastern Finland, a long-term prospective cohort study has suggested that low

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https://doi.org/10.1016/j.isci.2021.103191

Table 1. Demographic characteristics of the UK Biobank participants

Characteristics[a]	Total (N = 376,346)	Females (n = 202,177)	Males (n = 174,169)	p[b]
Age (years)	57.96 ± 7.95	57.75 ± 7.86	58.20 ± 8.04	<0.001
BMI	27.41 ± 4.75	27.04 ± 5.13	27.84 ± 4.23	<0.001
Drinking status				<0.001
Never	11,595 (3.08)	8,686 (4.30)	2,909 (1.67)	
Previous	12,834 (3.41)	7,229 (3.58)	5,605 (3.22)	
Current	351,917 (93.51)	186,262 (92.13)	165,655 (95.11)	
Smoking status				<0.001
Never	205,541 (54.62)	120,125 (59.42)	85,416 (49.04)	
Previous	132,721 (35.27)	64,539 (31.92)	68,182 (39.15)	
Current	38,084 (10.12)	17,513 (8.66)	20,571 (11.81)	

BMI, body mass index; SD, standard deviation.

[a]The data were summarized as median ±SD for continuous variables or as numbers (percentage) for categorical variables.

[b]p value were derived from t test for continuous variables, and chi-square test for the categorical variables, when compared the difference between females and males.

serum magnesium levels are independently associated with increasing both the total risk of fracture and the femoral fracture risk in middle-aged Caucasian men (Kunutsor et al., 2017). Using the method of meta-analysis and systematic reviews to evaluate the effects of magnesium supplementation on hypertension, a few studies have found that higher doses of magnesium lead to greater reductions in blood pressure (Lawton et al., 2017; Volpe, 2013).

Traditional epidemiological studies (such as cross-sectional, case-control, and cohort studies) into the effects of serum magnesium levels can be hindered by unmeasured and unknown factors, as well as potential confounding factors and reverse causation bias from outcomes that affect the serum magnesium levels. Moreover, a traditional epidemiological study design can test only one (or a limited number of) association(s) between the exposure and one (or a few) predefined outcome(s). In recent years, an integrating method known as Mendelian randomization and phenome-wide association study (MR-PheWAS) analysis has been proposed to build a hypothesis-searching approach that is aimed at exploring potential causal relationships between an exposure (using exposure-associated genetic loci as the instrumental variable) and a large range of phenome-wide disease outcomes in a high-throughput manner (Li et al., 2018b). This method allows for the rapid and effective evaluation or replication of potential health implications attributable to varying an exposure of interest found in epidemiological studies, as well as the ability to discover new relationships and generate new hypotheses for further targeted study (Denny et al., 2013).

However, there has been no systematic study assessing the causal effects of serum magnesium levels on multiple disease outcomes. Here, we performed an MR-PheWAS using the UK Biobank database to discover a wide range of disease outcomes related to genetic variations of serum magnesium levels and to investigate if any association is causal.

RESULTS

Demographic characteristics

The demographic data is shown in Table 1. The participants consisted of 202,177 females (53.72%) and 174,169 males (46.28%). Age, body mass index (BMI), drinking status, and smoking status were all different between females and males (p < 0.001).

PheWAS

Within the phenotypic data of the UK Biobank participants, we identified 307,580 hospital episode records, comprising 1,888 unique International Classification of Diseases coding systems (ICD-10) codes. After mapping diagnostic ICD-10 codes to phecodes and filtering out disease outcomes with less than 200 cases, the phenotypic data, consisting of 865 distinct phenotypes classified into 17 disease categories, were summarized. Finally, 601 phecodes (median number of cases = 1,357, ranging from 201 to 83,955) were included in

Table 2. The number of phenotypes and cases in each disease category

Disease categories	Phenotypes	Cases			
		Minimum	Median	Mean	Maximum
Circulatory system	53	222	1,792	6,365	83,955
Congenital anomalies	10	231	342	378	633
Dermatologic	34	272	1,148	1,961	8,506
Digestive	62	281	2,693	6,468	38,518
Endocrine/metabolic	34	207	786	4,250	42,989
Genitourinary	62	219	1,871	3,841	22,046
Hematopoietic	15	214	820	2,531	12,914
Infectious diseases	9	316	1,077	2,720	8,182
Injuries & poisonings	37	231	2,696	4,177	21,178
Mental disorders	25	211	790	2,825	33,250
Musculoskeletal	39	238	1,979	5,538	24,437
Neoplasms	64	207	947	3,067	33,250
Neurological	34	232	832	2,159	13,557
Pregnancy complications	27	201	920	1,276	6,388
Respiratory	40	201	1,483	4,599	36,623
Sense organs	45	201	834	2,149	17,917
Symptoms	11	418	6,593	10,707	48,335

After mapping diagnostic ICD-10 codes to phecodes (the mappings of phecodes are available at http://phewascatalog.org), 865 different phecodes were summarized and 601 phecodes were included in the PheWAS analyses after eliminating disease outcomes with low prevalence (cases <200).

PheWAS analysis (Table 2). A total of 19 pairs of genotype–phenotype associations then passed the significance threshold of 10% false discovery rate (FDR) correction in the total population PheWAS analysis with adjustment for covariates, as seen in Table 3 and Figure S1, including 10 disease groups (myeloproliferative disease, benign neoplasm of other parts of digestive system, gout and other crystal arthropathies, cataract, hypertension, other disorders of stomach and duodenum, miscarriage and stillbirth, arthropathy associated with infections, other arthropathies, and fracture of upper limb) and five disease outcomes (gout, essential hypertension, unspecified monoarthritis, arthropathy NOS, and fracture of radius and ulna). All the results of the PheWAS for each instrument single nucleotide polymorphisms (SNPs) are provided in Tables S1, S2, S3, S4, S5, and S6.

Further, we used the weighted genetic risk score (GRS) of serum magnesium levels to conduct the same PheWAS analysis. A total of 12 pairs of genotype–phenotype associations passed the significance threshold of 10% FDR correction in the total population PheWAS analysis with adjustment for covariates, as seen in Table 4 and Figure S2, including six diseases groups (fracture of upper limb, cataract, myeloproliferative disease, gout and other crystal arthropathies, degenerative skin conditions and other dermatoses, and other disorders of stomach and duodenum) and six disease outcomes (fracture of radius and ulna, inguinal hernia, polycythemia vera, gout, malignant neoplasm of female breast, and seborrheic keratosis).

The gender-stratified PheWAS analysis identified 6 pairs of genotype–phenotype association in males and 12 pairs of genotype–phenotype association in females (Table 3). When compared with the total population PheWAS analysis, four new pairs of association (migraine and renal colic in males, chronic renal failure and hematuria in females) were identified from the gender-stratified PheWAS analysis.

MR

We then conducted MR analysis using three methods (inverse-variance weighted [IVW], weighted median, and MR egger) to test whether magnesium levels were causally associated with the 20 disease groups/outcomes identified from PheWAS analysis using SNPs and GRS. At least one of three methods suggested a

Table 3. Genotype-phenotype associations identified by the PheWAS analyses

SNPs	Phenotypes	Descriptions	Groups	Total (n)	Cases (n)	OR (95% CI)	p	FDR-q[a]
Total population								
rs4072037_C	537	Other disorders of stomach and duodenum	Digestive	349,464	8,801	0.92 (0.89, 0.95)	2.89×10^{-8}	1.65×10^{-5}
	274	Gout and other crystal arthropathies	Endocrine/metabolic	376,346	4,016	1.10 (1.06, 1.15)	1.18×10^{-5}	0.002
	274.1	Gout	Endocrine/metabolic	376,346	4,016	1.10 (1.06, 1.15)	1.18×10^{-5}	0.002
	366	Cataract	Sense organs	376,346	24,571	0.96 (0.95, 0.98)	8.60×10^{-5}	0.011
	634	Miscarriage; stillbirth	Pregnancy complications	373,647	2,299	1.12 (1.06, 1.19)	1.13×10^{-4}	0.013
	211	Benign neoplasm of other parts of digestive system	Neoplasms	368,903	1,352	0.86 (0.80, 0.93)	1.56×10^{-4}	0.015
	803.2	Fracture of radius and ulna	Injuries & poisonings	373,683	6,549	0.94 (0.90, 0.97)	2.51×10^{-4}	0.018
	803	Fracture of upper limb	Injuries & poisonings	373,687	6,553	0.94 (0.91, 0.97)	2.58×10^{-4}	0.018
	200	Myeloproliferative disease	Neoplasms	373,256	715	0.83 (0.75, 0.93)	6.61×10^{-4}	0.042
	711	Arthropathy associated with infections	Musculoskeletal	351,723	424	1.24 (1.09, 1.42)	0.002	0.087
rs448378_G	401.1	Essential hypertension	Circulatory system	376,153	83,955	1.03 (1.02, 1.05)	8.86×10^{-9}	2.70×10^{-6}
	401	Hypertension	Circulatory system	376,346	84,148	1.03 (1.02, 1.05)	9.41×10^{-9}	2.70×10^{-6}
rs13146355_G	401	Hypertension	Circulatory system	376,346	84,148	1.03 (1.01, 1.04)	8.89×10^{-6}	0.003
	401.1	Essential hypertension	Circulatory system	376,153	83,955	1.03 (1.01, 1.04)	9.35×10^{-6}	0.003
rs3925584_T	401.1	Essential hypertension	Circulatory system	376,153	83,955	1.03 (1.02, 1.04)	7.74×10^{-6}	0.003
	401	Hypertension	Circulatory system	376,346	84,148	1.03 (1.01, 1.04)	8.82×10^{-6}	0.003
rs7965584_A	716	Other arthropathies	Musculoskeletal	373,592	22,293	1.09 (1.04, 1.13)	3.90×10^{-5}	0.009
	716.9	Arthropathy NOS	Musculoskeletal	373,592	22,293	1.09 (1.04, 1.13)	3.90×10^{-5}	0.009
	716.2	Unspecified monoarthritis	Musculoskeletal	373,466	22,167	1.08 (1.04, 1.13)	4.48×10^{-5}	0.009
Males								
rs4072037_C	274	Gout and other crystal arthropathies	Endocrine/metabolic	174,169	3,478	1.11 (1.06, 1.16)	1.95×10^{-5}	0.004
	274.1	Gout	Endocrine/metabolic	174,169	3,478	1.11 (1.06, 1.16)	1.95×10^{-5}	0.004
rs11144134	340	Migraine[b]	Neurological	171,050	759	0.72 (0.61, 0.84)	4.26×10^{-5}	0.019
	594.8	Renal colic[b]	Genitourinary	170,775	1,277	0.78 (0.69, 0.89)	1.63×10^{-4}	0.036
rs3925584_T	401.1	Essential hypertension	Circulatory system	174,066	45,525	1.04 (1.02, 1.06)	2.30×10^{-6}	0.001
	401	Hypertension	Circulatory system	174,169	45,628	1.04 (1.02, 1.06)	2.68×10^{-6}	0.001
Females								
rs4072037_C	537	Other disorders of stomach and duodenum	Digestive	187,969	5,049	0.90 (0.87, 0.94)	7.36×10^{-7}	3.41×10^{-4}
	211	Benign neoplasm of other parts of digestive system	Neoplasms	199,087	827	0.81 (0.74, 0.90)	4.04×10^{-5}	0.009
	634	Miscarriage; stillbirth	Pregnancy complications	199,479	2,298	1.12 (1.06, 1.19)	1.28×10^{-4}	0.020
	803	Fracture of upper limb	Injuries & poisonings	200,676	4,879	0.93 (0.90, 0.97)	0.001	0.067
	803.2	Fracture of radius and ulna	Injuries & poisonings	200,673	4,876	0.93 (0.90, 0.97)	0.001	0.067
	366	Cataract	Sense organs	202,177	13,738	0.96 (0.93, 0.98)	0.001	0.084
rs448378_G	401.1	Essential hypertension	Circulatory system	202,087	38,430	1.05 (1.03, 1.06)	2.51×10^{-7}	6.39×10^{-5}
	401	Hypertension	Circulatory system	202,177	38,520	1.05 (1.03, 1.06)	2.76×10^{-7}	6.39×10^{-5}
rs13146355_G	401	Hypertension	Circulatory system	202,177	38,520	1.03 (1.02, 1.05)	1.47×10^{-4}	0.043

Table 3. Continued

SNPs	Phenotypes	Descriptions	Groups	Total (n)	Cases (n)	OR (95% CI)	p	FDR-q[a]
	401.1	Essential hypertension	Circulatory system	202,087	38,430	1.03 (1.02, 1.05)	1.88×10^{-4}	0.043
	585.3	Chronic renal failure [CKD][b]	Genitourinary	199,105	2,989	0.91 (0.87, 0.96)	0.001	0.078
	593	Hematuria[b]	Genitourinary	199,950	6,479	1.06 (1.03, 1.10)	0.001	0.078

Abbreviations: CI, confidence interval; NOS, not otherwise specified; OR, odds ratio; PheWAS, phenome-wide association study.
Notes: The PheWAS analysis was adjusted by age, sex, BMI, assessment center, and the first 15 genetic principal components.
[a]Significance threshold of a lower than 10% false discovery rate after correcting the multiple testing.
[b]When compared with the total population PheWAS analyses, significant pairs of associations were newly identified from the gender-stratified PheWAS analyses.

potential causal association of serum magnesium levels for 11 out of 20 disease outcomes (Table 5), including five disease groups: myeloproliferative disease ($OR_{IVW} = 3.49 \times 10^5$, 95% CI: 24.92, 4.88×10^9; $OR_{weighted\ median} = 3.89 \times 10^6$, 95% CI: 194.28, 7.81×10^{10}), gout and other crystal arthropathies ($OR_{weighted\ median} = 0.00$, 95% CI: 0.00, 0.06), cataract ($OR_{IVW} = 9.24$, 95% CI: 1.53, 55.61; $OR_{weighted\ median} = 24.93$, 95% CI: 4.55, 136.63), degenerative skin conditions and other dermatoses ($OR_{IVW} = 185.81$, 95% CI: 1.81, 19,081.09; $OR_{weighted\ median} = 179.93$, 95% CI: 2.93, 11,038.98), and fracture of upper limb ($OR_{IVW} = 106.57$, 95% CI: 10.67, 1,064.37; $OR_{weighted\ median} = 69.45$, 95% CI: 9.00, 1,209.85); and six disease outcomes: malignant neoplasm of female breast ($OR_{IVW} = 16.39$, 95% CI: 2.52, 106.34; $OR_{weighted\ median} = 19.96$, 95% CI: 2.01, 198.35), polycythemia vera ($OR_{IVW} = 1.64 \times 10^7$, 95% CI: 1,388.27, 1.94×10^{11}; $OR_{weighted\ median} = 1.76 \times 10^7$, 95% CI: 81.73, 3.78×10^{12}), gout ($OR_{weighted\ median} = 0.00$, 95% CI: 0.00, 0.06), inguinal hernia ($OR_{IVW} = 0.09$, 95% CI: 0.01, 1.00; $OR_{weighted\ median} = 0.10$, 95% CI: 0.01, 0.83), seborrheic keratosis ($OR_{IVW} = 187.69$, 95% CI: 1.81, 19,450.49; $OR_{weighted\ median} = 180.37$, 95% CI: 3.32, 9,788.32), and fracture of radius and ulna ($OR_{IVW} = 109.18$, 95% CI: 10.92, 1,091.13; $OR_{weighted\ median} = 70.86$, 95% CI: 3.68, 1,365.13).

The gender-stratified analysis indicated differences in MR estimated effects between males and females with the exceptions of hypertension and essential hypertension (Table 5). For males, magnesium levels were associated with one disease group: gout and other crystal arthropathies ($P_{weighted\ median} < 0.001$); and three disease outcomes: gout ($P_{weighted\ median} = 0.001$), essential hypertension ($P_{weighted\ median} = 0.038$), and renal colic ($P_{weighted\ median} = 0.032$, $P_{Egger} = 0.012$). Meanwhile, in females, there were significant associations with four disease groups: cataract ($P_{weighted\ median} = 0.002$), other disorders of stomach and duodenum ($P_{weighted\ median} = 0.031$, $P_{Egger} = 0.046$), miscarriage and stillbirth ($P_{IVW} = 0.049$, $P_{weighted\ median} = 0.005$), and fracture of upper limb ($P_{IVW} < 0.001$, $P_{weighted\ median} = 0.001$); and one outcome: fracture of radius and ulna ($P_{IVW} < 0.001$, $P_{weighted\ median} < 0.001$).

Pleiotropy and sensitivity analyses

We undertook the MR weighted median analysis and MR Egger analysis to correct for possible pleiotropic effects of multiple instruments (Table 5). After balancing pleiotropic effects in the MR weighted median analysis, all the results were consistent with the IVW analysis of total population. However, using the MR Egger analysis, none of the results were considered to be causally associated with higher serum magnesium levels without pleiotropic effects (all $P_{pleiotropy} > 0.05$).

The protein-protein interaction (PPI) network

We selected 15 serum magnesium-associated genes (including the instrumental variable [IV] SNPs located genes and the top ten associated genes) to construct the PPI network. However, for 11 disease outcomes identified by MR analysis, only the top ten cataract-associated genes were found in the GeneCards website (Table 6). The PPI network demonstrated an interaction between the serum magnesium-associated gene *DCDC1* and the cataract-associated gene *PAX6* (Figure 1).

DISCUSSION

This is the first MR-PheWAS investigating the totality of health effects associated with serum magnesium levels. We found evidence of a detrimental effect of higher magnesium status on risk of malignant neoplasm of female breast, myeloproliferative disease, polycythemia vera, cataract, degenerative skin conditions and other dermatoses, seborrheic keratosis, and fracture of upper limb (fracture of radius and ulna). Contrarily, our MR-PheWAS provided with evidences of a protective effect of higher magnesium status on

Table 4. The results of the PheWAS analyses for magnesium-GRS in the total population

Phenotypes	Descriptions	Groups	Total (n)	Cases (n)	Or (95% CI)	p	FDR-q[a]
803.2	Fracture of radius and ulna	Injuries & poisonings	373,683	6,549	127.87 (12.85, 1,272.43)	3.5×10^{-4}	0.011
803	Fracture of upper limb	Injuries & poisonings	373,687	6,553	124.84 (12.55, 1,241.51)	3.81×10^{-5}	0.011
550.1	Inguinal hernia	Digestive	342,594	16,575	0.06 (0.01, 0.28)	2.52×10^{-4}	0.033
366	Cataract	Sense organs	376,346	24,571	9.61 (2.76, 33.44)	3.73×10^{-4}	0.033
200	Myeloproliferative disease	Neoplasms	373,256	715	2.64×10^5 (271.59, 2.51×10^8)	3.76×10^{-4}	0.033
200.1	Polycythemia vera	Neoplasms	369,575	395	1.47×10^7 (1.43×10^3, 1.52×10^{11})	4.65×10^{-4}	0.033
274	Gout and other crystal arthropathies	Endocrine/metabolic	376,346	4,016	0.01 (0.00, 0.10)	4.65×10^{-4}	0.033
274.1	Gout	Endocrine/metabolic	376,346	4,016	0.01 (0.00, 0.10)	4.65×10^{-4}	0.033
174.11	Malignant neoplasm of female breast	Neoplasms	368,619	10,429	21.57 (3.45, 134.83)	1.02×10^{-3}	0.065
702.2	Seborrheic keratosis	Dermatologic	376,346	3,356	187.86 (7.69, 4,588.89)	1.32×10^{-3}	0.070
702	Degenerative skin conditions and other dermatoses	Dermatologic	371,673	3,356	187.23 (7.66, 4,577.17)	1.34×10^{-3}	0.070
537	Other disorders of stomach and duodenum	Digestive	349,464	8,801	23.19 (3.15, 170.66)	2.02×10^{-3}	0.097

Abbreviations: CI, confidence interval; FDR, false discovery rate; GRS, genetic risk score; NOS, not otherwise specified; OR, odds ratio; PheWAS, phenome-wide association study.

Notes: The PheWAS analysis was adjusted by age, sex, BMI, assessment center, and the first 15 genetic principal components.

[a]Significance threshold of a lower than 10% false discovery rate after correcting the multiple testing.

risk of gout and other crystal arthropathies (gout) as well as inguinal hernia. In addition, our study indicates gender-specific effects of nine disease groups/outcomes in MR estimated effects.

Consistent with our findings for malignant neoplasm of female breast, an MR study using the data from the Breast Cancer Association Consortium suggested that magnesium is positively associated with breast cancer risk (Papadimitriou et al., 2021). In contrast, a cohort study reported no significant difference between magnesium consumption and breast cancer risk (Li et al., 2011). Previous studies have shown that increased concentrations of magnesium in breast cancer cells is capable of promoting tumor progression by regulating enzymes associated with energy generation, which was required for cell adhesion and cancer metastasis (Mendes et al., 2018). Animal studies have suggested that magnesium is protective in the early stages of chemical carcinogenesis, while also promoting tumor growth (Castiglioni and Maier, 2011). Our findings should be further evaluated in observational and interventional designs.

There is a lot of evidence suggesting that magnesium is good for bone health; however, the vast majority of research has investigated dietary magnesium as an exposure rather than investigating serum magnesium (Kunutsor et al., 2017). Even though high dietary magnesium intake is associated with higher bone mineral density (Ryder et al., 2005), the conclusion for a benefit in fracture risk remains controversial. A meta-analysis suggested that high dietary magnesium intake does not reduce the fracture risk (Farsinejad-Marj et al., 2016). Consistent with our results, the Women's Health Initiative Observational Study showed that magnesium intake exceeding the recommended dietary allowance is linked with an increased risk of forearm and wrist fractures (Orchard et al., 2014). Moreover, because magnesium has anti-calcification properties, excess magnesium accumulation in the bone might be harmful (Cunningham et al., 2012). Whether the association of serum magnesium levels and risk of fracture reflects a real correlation needs to be further confirmed. Most observational epidemiological studies of magnesium dietary intake have been limited by misclassification bias because of the fact that foods containing magnesium are often rich in calcium and potassium, which interact with other trace elements to keep bone health and, hence, make it difficult

Table 5. The results of two-sample MR analyses

Phenotypes	Descriptions	IVW OR (95% CI)	p	$P_{heterogeneity}$	Weighted median OR (95% CI)	p	MR Egger OR (95% CI)	p	$P_{pleiotropy}$
Total population									
174.11	Malignant neoplasm of female breast	16.39 (2.52, 106.34)	0.003	0.409	19.96 (2.01, 198.35)	0.011	104.92 (0.35, 31,628.18)	0.185	0.534
200	Myeloproliferative disease	3.49×10^5 (24.92, 4.88×10^9)	0.009	0.098	3.89×10^6 (194.28, 7.81×10^{10})	0.003	768.00 (0.00, 8.94×10^{15})	0.687	0.693
200.1	Polycythemia vera	1.64×10^7 (1.39×10^3, 1.94×10^{11})	<0.001	0.503	1.76×10^7 (81.73, 3.78×10^{12})	0.008	98.54 (0.00, 4.76×10^{13})	0.755	0.403
274	Gout and other crystal arthropathies	0.01 (0.00, 7.69)	0.162	<0.001	0.00 (0.00, 0.06)	0.002	0.00 (0.00, 5.37×10^6)	0.561	0.844
274.1	Gout	0.01 (0.00, 7.69)	0.162	<0.001	0.00 (0.00, 0.06)	0.002	0.00 (0.00, 5.37×10^6)	0.561	0.844
366	Cataract	9.24 (1.53, 55.61)	0.015	0.065	24.93 (4.55, 136.63)	<0.001	291.00 (3.12, 27,124.93)	0.070	0.187
550.1	Inguinal hernia	0.09 (0.01, 1.00)	0.049	0.023	0.10 (0.01, 0.83)	0.033	1.11 (0.00, 1890.45)	0.979	0.512
702	Degenerative skin conditions and other dermatoses	185.81 (1.81, 19,081.09)	0.027	0.062	179.93 (2.93, 11,038.98)	0.013	1.86 (0.00, 2.54×10^6)	0.935	0.533
702.2	Seborrheic keratosis	187.69 (1.81, 19,450.49)	0.027	0.061	180.37 (3.32, 9,788.32)	0.011	1.85 (0.00, 2.59×10^6)	0.936	0.533
803	Fracture of upper limb	106.57 (10.67, 1,064.37)	<0.001	0.738	69.45 (3.99, 1,209.85)	0.004	6,846.11 (9.00, 5.21×10^6)	0.059	0.260
803.2	Fracture of radius and ulna	109.18 (10.92, 1,091.13)	<0.001	0.731	70.86 (3.68, 1,365.13)	0.005	7,279.51 (9.56, 5.54×10^6)	0.058	0.256
Males									
274	Gout and other crystal arthropathies	0.01 (1.53×10^{-6}, 17.02)	0.202	5.49×10^{-6}	0.00 (2.25×10^6, 0.03)	0.001	5.37×10^{-4} (2.61×10^{-15}, 1.11×10^8)	0.601	0.866
274.1	Gout	0.01 (1.53×10^{-6}, 17.02)	0.202	5.49×10^{-6}	0.00 (1.92×10^6, 0.04)	0.001	5.37×10^{-4} (2.61×10^{-15}, 1.11×10^8)	0.601	0.866
340	Migraine	299.76 (5.42×10^{-4}, 1.66×10^8)	0.398	0.001	22.04 (0.00, 1.82×10^5)	0.502	1.89×10^9 (1.77×10^{-8}, 2.02×10^{26})	0.346	0.451
401	Hypertension	3.26 (0.16, 66.61)	0.443	2.40×10^{-7}	4.07 (0.89, 18.60)	0.070	2.96×10^2 (0.06, 1.49×10^6)	0.261	0.331
401.1	Essential hypertension	3.27 (0.16, 68.13)	0.445	1.93×10^{-7}	4.49 (1.09, 18.51)	0.038	3.06×10^2 (0.06, 1.63×10^6)	0.261	0.331
594.8	Renal colic[a]	1,379.50 (0.14, 1.34×10^7)	0.123	0.006	2,388.81 (1.97, 2.90×10^6)	0.032	1.64×10^{14} (7.08×10^7, 3.81×10^{20})	0.012	0.022
Females									
211	Benign neoplasm of other parts of digestive system	93.39 (1.70×10^{-4}, 5.14×10^7)	0.501	0.001	1.24 (6.80×10^{-6}, 2.27×10^5)	0.972	2.81×10^{12} (0.00, 3.39×10^{27})	0.181	0.221
366	Cataract	11.03 (0.89, 1.36×10^2)	0.061	0.047	31.99 (3.44, 2.97×10^2)	0.002	7.59×10^2 (0.84, 6.89×10^5)	0.129	0.264

(Continued on next page)

Table 5. Continued

Phenotypes	Descriptions	IVW			Weighted median		MR Egger		
		OR (95% CI)	p	$P_{heterogeneity}$	OR (95% CI)	p	OR (95% CI)	p	$P_{pleiotropy}$
401	Hypertension	0.46 (0.02, 13.67)	0.652	8.25×10^{-9}	2.64 (0.65, 10.73)	0.174	1.97×10^3 (2.61, 1.49×10^6)	0.088	0.058
401.1	Essential hypertension	0.46 (0.02, 13.67)	0.651	8.54×10^{-9}	2.63 (0.65, 10.60)	0.174	1.93×10^3 (2.47, 1.51×10^6)	0.090	0.059
537	Other disorders of stomach and duodenum	96.95 (0.67, 1.40×10^4)	0.071	0.003	127.65 (1.56, 1.04×10^4)	0.031	7.71×10^6 (1.44 × 10^{20}, 4.13×10^{11})	0.046	0.096
585.3	Chronic renal failure (CKD)	16.55 (0.03, 1.04×10^4)	0.393	0.003	0.14 (0.00, 16.54)	0.422	6.29×10^{-4} (1.09 × 10^{-11}, 3.62×10^4)	0.464	0.300
593	Hematuria	0.57 (0.01, 22.45)	0.762	0.029	2.60 (0.15, 45.37)	0.513	3.02×10^2 (0.02, 6.00×10^6)	0.321	0.256
634	Miscarriage; stillbirth	3.00×10^{-3} (1.06×10^{-5}, 0.96)	0.049	0.067	2.62×10^{-4} (8.25×10^{-7}, 0.08)	0.005	6.53×10^{-7} (6.32 × 10^{-14}, 6.75)	0.159	0.333
803	Fracture of upper limb	205.22 (14.14, 2.98×10^3)	<0.001	0.552	367.00 (11.56, 1.17×10^4)	0.001	3.16×10^4 (14.19, 7.03×10^7)	0.058	0.244
803.2	Fracture of radius and ulna	205.22 (14.14, 2.98×10^3)	<0.001	0.535	421.34 (15.69, 1.17×10^4)	3.19×10^{-4}	3.29×10^4 (14.77, 7.34×10^7)	0.057	0.241

Abbreviations: CI, confidence interval; IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; PheWAS, phenome-wide association study.
[a]When compared with the total population MR analyses, significant pairs of associations were newly identified from the gender-stratified MR analyses.

to assess the individual effect of each nutrient. In addition, many factors have been shown to play significant roles in bone health, such as gender, aging, exercise, hormones, and heritability (Martini, 1999).

Magnesium, presented mainly in cornea, lens, retina, vitreous body, and anterior chamber in the eyes, is essential for the lens to maintain integrity of its structure and normal function (Agarwal et al., 2012; Li et al., 2018a). A high level of Mg^{2+} exists in photoreceptors in the lens, even in the axial regions (Kirkpatrick, 1920). The consequences of imbalance in magnesium homeostasis may influence the cellular and molecular functions and may form the basis of some pathological conditions. Magnesium has been reported to enhance oxidative stress in the lens by increasing the production of free radicals and depleting antioxidant defenses (Agarwal et al., 2013). Moreover, since ATPase function appears to be essential to the lens, the role of magnesium in Na^+-K^+-ATPase and Ca^{2+}-ATPase activities may be important for ion transport in the lens (Agarwal et al., 2013). Notably, animal studies have shown that administration of deep-sea water, containing 200 mg/L of magnesium, can delay the development of cataracts in cataract-prone rats, although this cataract development did not improve with further increases in the magnesium levels (Shumiya, 1995). It is speculated that high levels of magnesium might have detrimental effects on the lens. Although the mechanisms involved in magnesium homeostasis and the role of magnesium deficiency in the pathogenesis of cataracts needs to be further explored, our findings via the PPI network may support this possibility. The PPI network demonstrated an interaction between the serum magnesium-associated gene *DCDC1* and the cataract-associated gene *PAX6*, which are both involved in the regulation of cell division. Mutations in *PAX6* gene, known genetic alterations causing varieties of autosomal-dominant ocular malformations, can lead to aniridia as the major clinical signs (Lima Cunha et al., 2019; Nieves-Moreno et al., 2021). Researchers have found that the 566 kb hemizygous deletion of chromosome 11p13 downstream of *PAX6* gene should be the cause of the familial aniridia (Cheng et al., 2011). In addition, the prior studies have also shown that 11p13 interstitial deletion (including *DCDC1* gene) can affect the downstream transcription of *PAX6*, whereas this effect would result in the occurrences of aniridia and eye deformities (Balay et al., 2016).

Some studies have found positive links between magnesium and a reduced risk of knee osteoarthritis (Qin et al., 2012; Veronese et al., 2017). Magnesium supplementation in elderly patients may reduce the risk of knee osteoarthritis. Magnesium supplementation may also improve the symptoms and progression

Table 6. The serum magnesium-associated and cataract-associated genes included in the PPI network diagram

Traits	Serum magnesium-associated genes	Relevance scores	Disease	Disease-associated genes[c]	Relevance scores
Serum magnesium (GeneCards)[a]	CNNM2	30.49	Cataract	CRYAA/HSPB4	111.9
	TRPM6	27.16		GJA8	90.66
	CLDN16	19.35		GJA3	81.45
	PTH	9.39		EPHA2	75.87
	PCBD1	9.39		CRYGD	75.42
	TRPM7	9.39		OPA3	74.75
	CLDN19	9.39		CRYBB2	73.39
	PEX1	8.13		FTL	72.61
	SBDS	8.13		CRYBB1	72.55
	PEX26	8.13		PAX6	69.94
Serum magnesium (IV)[b]	TRPM6	27.16			
	MUC1	2.89			
	MECOM	2.12			
	SHROOM3	2.12			
	ATP2B1	2.12			
	DCDC5/DCDC1	2.12			

Abbreviations: IV, instrumental variable; PPI, protein-protein interaction.

[a]The top ten serum magnesium-associated genes were searched for using the GeneCards website (https://www.genecards.org/).

[b]The serum magnesium-associated SNPs (using as IV in the MR-PheWAS analyses) located genes.

[c]The top ten cataract-associated genes were searched for using the GeneCards website (https://www.genecards.org/).

of knee osteoarthritis (Wu et al., 2019). Although there has been no traditional epidemiological study of the relationship between magnesium and gout, a MR study suggested a positive link with the risk of gout (Cheng et al., 2019). The mechanism underlying these relationships needs to be further studied.

Although no epidemiological studies concerning the associations between magnesium and myeloproliferative disease, inguinal hernia, or seborrheic keratosis have been reported, our study provides some suggestive evidence. Further research on these diseases will be well worth exploring; independent cohort studies and functional studies are warranted to verify these relatively novel associations. No previous observational studies have reported gender difference in the association between magnesium levels and the development of the above diseases, nor have any studies addressed these sex differences using an MR approach to negate the influence of environmental confounders. Our study identified a few diseases, including cataract, fracture of upper limb, and other disorders of stomach and duodenum, that are potentially causally associated with genetic variations of magnesium levels only in females, whereas renal colic and gout and other crystal arthropathies were seen to be associated with magnesium only in males. The biological mechanism(s) by which magnesium levels are linked to certain diseases do not seem to be consistent between males and females and remain to be further studied.

A prior study utilized the MR method to examine the association of genetically magnesium with the risk of 9 chronic diseases, consisting of type 2 diabetes, osteoporosis, rheumatoid arthritis, gout, Parkinson's disease, Alzheimer's disease, major depressive disorder, bipolar disorder, and schizophrenia (Cheng et al., 2019). However, the present study conducted a hypothesis-free investigation of the causal effects of magnesium levels more broadly across the human phenome, thus contributing to the discovery of new relations. Using SNPs that are strongly associated with blood magnesium levels as instrument variants that are randomly assorted at conception; we tested the cumulative lifetime effects of genetically determined variation across more than 700 disease outcomes. One of the main challenges to the MR method is deciphering which effects are attributable to bias owing to pleiotropic SNPs; we utilized the weighted median and Egger methods to solve this problem (Bowden et al., 2016).
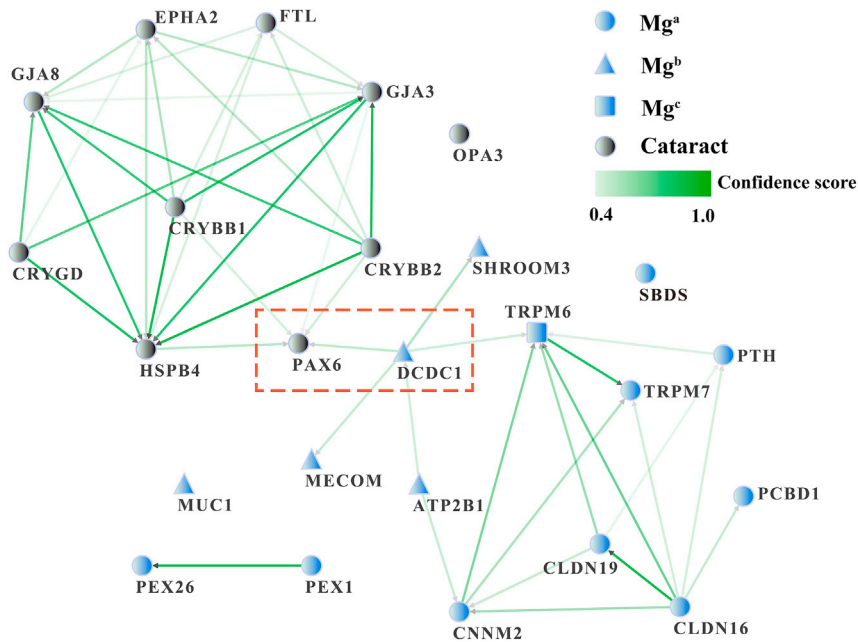
Figure 1. Diagram of the interactions between the serum magnesium-associated genes and the cataract-associated genes

Mg[a]: the top ten associated genes of serum magnesium were searched for using the GeneCards website (https://www.genecards.org/). Mg[b]: the instrumental variable SNPs located genes of serum magnesium. Mg[c]: the gene is the top ten genes as well as the instrumental variable SNPs located genes of serum magnesium. All confidence scores range from 0.4 to 1, while one is the highest. The darker the green line with the arrow, the higher the confidence score, indicating a stronger interaction between the two genes.

Recognizing and understanding the basic pathophysiological mechanisms of disease occurrence and development is of great significance for formulating future pharmacological strategies. In addition, magnesium supplementation may have therapeutic value in preventing the occurrence and progression of diseases associated with magnesium deficiency, whereas reducing magnesium status may have therapeutic value in preventing diseases associated with excessive magnesium. Notably, our findings of interaction between the serum magnesium-associated gene *DCDC1* and the cataract-associated gene *PAX6* may provide new targets for promoting the treatments of cataracts using magnesium intervention.

Limitations of the study

This study also has limitations. First, we used Hospital Exchange-information System data, which provided a rich source of clinical outcomes that were related to genetic data of UK Biobank participants, but may also introduce misclassification bias (Padmanabhan et al., 2019). Second, insufficient statistical power may also lead to false negative results in our study. The previously reported effects of serum magnesium on risk of bipolar disorder and coronary artery disease risk by MR were not statistically significant in our analyses after adjusting for multiple testing (Cheng et al., 2019; Larsson et al., 2018). Using the interim release data of UK Biobank and focusing on a very homogeneous population (Caucasian based on genetic information) limited the power of our study. Moreover, to avoid information bias, we did not analyze the self-reported data from UK Biobank, although this may influence the comprehensiveness of PheWAS and decrease the precision of MR estimates. Last, because the MR estimates correlate with slight change in serum magnesium in the normal range rather than at extremes of magnesium deficiency or excess, caution must be taken when extrapolating the findings of MR.

Overall, our MR-PheWAS study supports a causal effect of serum magnesium on several clinically relevant disease outcomes, including: neoplasms; endocrine/metabolic, sensory organ, circulatory system, digestive and musculoskeletal diseases; pregnancy complications; injuries; and poisonings. Considering that serum magnesium is modifiable, exploring whether regulation of serum levels can be used to optimize health outcomes seems beneficial.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND SUBJECT DETAILS
- METHOD DETAILS
  - Genetic instruments for magnesium
  - PheWAS
  - MR
  - Pleiotropy and sensitivity analyses
  - The PPI network
- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.103191.

AUTHOR CONTRIBUTIONS

Conceptualization, Data Curation and Funding Acquisition, X.B.Y. and Z.N.M.; Writing – Original Draft and Formal Analysis, L.M.L. and W.J.Y.; Methodology, L.L.H. and X.M.F.; Software, H.C. and X.T.G.; Visualization, G.H.Z. and Y.L.T.; Writing – Review & Editing, L.M.L. and W.J.Y.; Validation, L.LX., C.Q.L. and X.C.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R software	The R Core Team	https://www.r-project.org/
PheWAS package	Denny et al., 2013;	https://github.com/PheWAS/PheWAS
TwoSampleMR package	Burgess et al., 2015; Burgess et al., 2017; Palmer et al., 2012	https://mrcieu.github.io/TwoSampleMR/articles/exposure.html
Cytoscape	Shannon et al., 2003; Otasek et al., 2019	https://cytoscape.org/
Other		
Ensembl database	Howe et al., 2021	http://grch37.ensembl.org/Homo_sapiens/Info/Index
STRING	Szklarczyk et al., 2021	https://string-db.org/
GeneCards	Stelzer et al., 2016	https://www.genecards.org/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Prof. Xiaobo Yang (yangx@gxmu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The raw data reported in this study cannot be deposited in a public repository because of the UK Biobank Committee stipulations. To request access, please login the UK Biobank official website to apply (https://www.ukbiobank.ac.uk/). This paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Our study was restricted to participants of Caucasian descent from UK Biobank (Sudlow et al., 2015), a prospective cohort with a total of 502,505 participants aged 40-69 years and recruited from 22 assessment centers throughout the UK between 2006 and 2010 at baseline, while relatives with a kinship coefficient of > 0.0884 were randomly excluded. Finally, a total of 376,346 participants consisted of 202,177 females (53.72%) and 174,169 males (46.28%) were enrolled in the analyses. UK Biobank has approval from the North West Multi-centre Research Ethics Committee (IRAS project ID: 299116), which covers the UK. The informed consent was obtained from all subjects. Additionally, this study has approval from the UK Biobank Ethics and Governance Council (Approval No. 56902).

METHOD DETAILS

Genetic instruments for magnesium

We selected six magnesium-associated SNPs as genetic instruments, which was based on a genome-wide association study (GWAS) performed by the International Cohorts for Heart and Aging Research in Genomic Epidemiology Alliance on 23,829 European subjects (combined Discovery [N = 15,366] and Replication [N = 8,463] cohorts) (Guo et al., 2020; Meyer et al., 2010). The six identified SNPs comprised: rs4072037 in Mucin1 (*MUC1*) gene, rs7965584 near ATPase plasma membrane Ca^{2+} transporting 1 (*ATP2B1*) gene, rs3925584 near the doublecortin domain containing 5 (*DCDC5*) gene, rs11144134 in transient receptor potential cation channel subfamily M member 6 (*TRPM6*) gene, rs13146355 in shroom family member 3 (*SHROOM3*) gene, and rs448378 in MDS1 and EVI1 complex locus (*MECOM*) gene. All SNPs were at a genome-wide significance level (p < 5 × 10^{-8}). All six of these SNPs have previously been shown

to be strong instruments for MR analysis as measured by F-statistics > 10 (Guo et al., 2020) and collectively explain approximately 1.62% of the variation in serum magnesium levels (Table S7). We used six serum magnesium-associated SNPs to construct a weighted GRS as a proxy for serum magnesium levels.

PheWAS

We used the WHO's ICD-10 to define the case and control groups. Both incident and prevalent cases were included, but not self-reported diagnoses. We focused on phenotypic data sets of inpatient hospital episode records in the UK Biobank. In PheWAS analysis, we individually used six magnesium-associated SNPs to scan across a wide range of disease outcomes defined by the phecode system (Denny et al., 2013). Additionally, we performed the same PheWAS using serum magnesium-associated GRS. The case groups were identified as individuals having at least one documented event, while the control groups were those without any record of this outcome or its related phecodes (Li et al., 2018b). Next, a series of case-control tests were performed for each phecode, and logistic regression analysis was generated for each instrument SNP separately across all phecodes, adjusting for age, sex, BMI, assessment center, and the first 15 genetic principal components. To ensure statistical power, the PheWAS analysis was only performed for phecode with 200 or more cases, which was suggested based on a simulation of power estimates for PheWAS analysis (Verma et al., 2018). We used the threshold of lower than 10% FDR to account for multiple testing, when the p-value less than 0.05 was considered statistically significant (Zhu et al., 2011).

MR

To explore if there were any causal effects on disease outcomes identified in the PheWAS analysis, IVW meta-analysis of MR estimates for all six instrument SNPs was performed to derive the overall MR estimate for the effect of magnesium on the risk of each considered outcome (Burgess et al., 2015; Palmer et al., 2012).

Pleiotropy and sensitivity analyses

We used the Ensembl database (http://grch37.ensembl.org/Homo_sapiens/Info/Index) to search for secondary phenotypes associated with each magnesium-associated SNP (Howe et al., 2021), and to exclude possible pleiotropic effects by manually removing these SNPs from the MR analyses (Table S7). Additionally, the MR- Egger method, which allows the intercept to be freely estimated as an indicator of average pleiotropic bias, was performed to correct for any potential pleiotropic effects in the causal estimates (Bowden et al., 2015; Burgess and Thompson, 2017). We also conducted the weighted median to further ensure the robust exclusion of pleiotropic instruments (Bowden et al., 2016).

The Cochran's Q statistic was then applied to evaluate heterogeneity in IVW estimates (Burgess et al., 2017; Egger et al., 1997; Huang et al., 2019). Moreover, to account for any difference between male and female gender, we performed PheWAS and MR analyses by gender stratification.

The PPI network

To explore the interactions between serum magnesium-associated genes and disease-associated genes, we used STRING (https://string-db.org/) and Cytoscape (https://cytoscape.org/) to construct a PPI network (Otasek et al., 2019; Shannon et al., 2003; Szklarczyk et al., 2021), using the IV SNPs located genes and the top ten associated genes of serum magnesium and disease outcomes. The top ten associated genes of serum magnesium and disease outcomes were searched for using the GeneCards website (https://www.genecards.org/) (Stelzer et al., 2016).

QUANTIFICATION AND STATISTICAL ANALYSIS

When compared the difference between females and males, t-test was used for continuous variables, and chi-square test for the categorical variables in Table 1. Regarding the MR-PheWAS analyses to estimate the causal effects of serum magnesium levels on multiple disease outcomes, we used R software by PheWAS package (https://github.com/PheWAS/PheWAS) and TwoSampleMR package (https://mrcieu.github.io/TwoSampleMR/articles/exposure.html) in Tables 3, 4, and 5, Figures S1 and S2, and Tables S1, S2, S3, S4, S5, and S6.

ADDITIONAL RESOURCES

This study was based on data obtained from a prospective cohort study: UK Biobank, an open access database to any bona fide researcher who wishes to use it to conduct health-related research for the benefit of the public, after being approved from the UK Biobank Ethics and Governance Council (https://www.ukbiobank.ac.uk/). At baseline, a total of 502,505 participants aged 40–69 years were recruited from 22 assessment centers throughout the UK between 2006 and 2010 (Sudlow et al., 2015). The cohort provided a wide range of self-reported baseline information, including data of health, lifestyle, diseases outcome and genome-wide genotyping (Bycroft et al., 2018).